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The portrait of anxiety

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is often complicated

With associated depressive symptoms.

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
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The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: *General.* Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n=	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	6%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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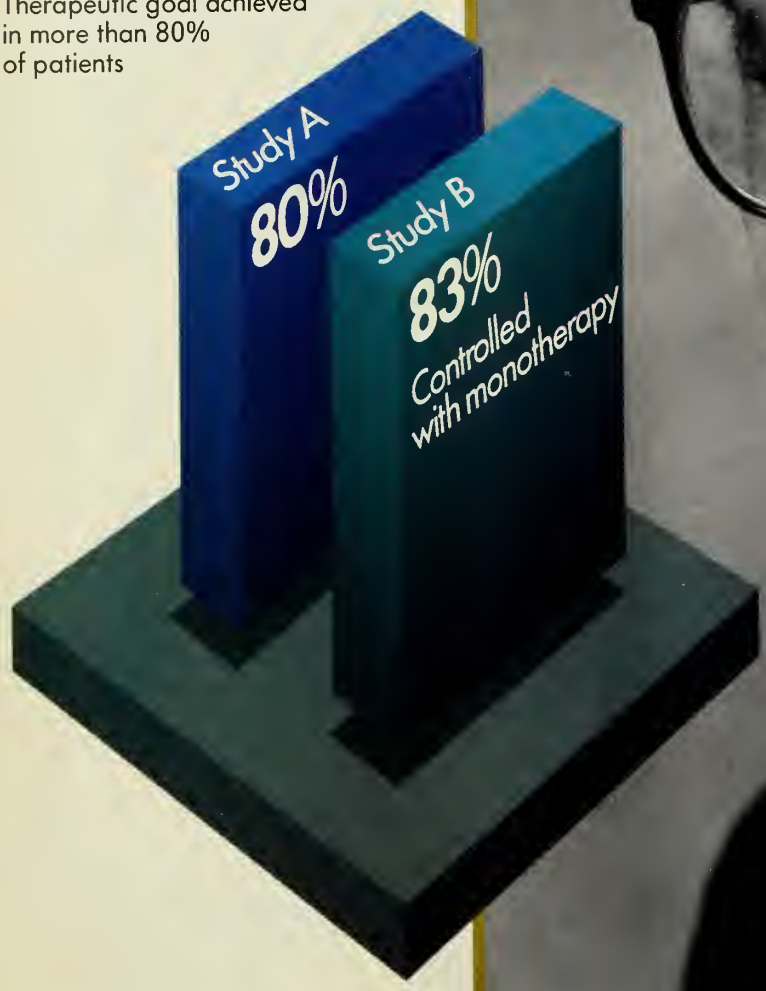

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Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence. 5/9/88 • C88-W5282V-1

References: **1.** Reinfrank J, Eckardt A, Hohn K-J: A long-term multicentre study of veropamil SR 240 mg in hypertension, in Fleckenstein A, Lorogh JH (eds): *Hypertension—The Next Decode: Veropomil in Focus.* New York, Churchill Livingstone, 1987, pp 307–313. **2.** Doto on file, G.D. Searle & Co. **3.** Baird MG, Bentley-Toylor MM, Carruthers SG, et ol: A study of efficocy, tolerance ond complionce of once-doily versus twice-doily metoprolol (Betoloc®) in hypertension. *Clin Invest Med* 1984;7:95–102. **4.** Cubeddu LX, Arondo J, Singh B, et ol: A comporison of veropamil ond propranolol for the initiol treatment of hypertension: Raciol differences in response. *JAMA* 1986;256:2214–2221.

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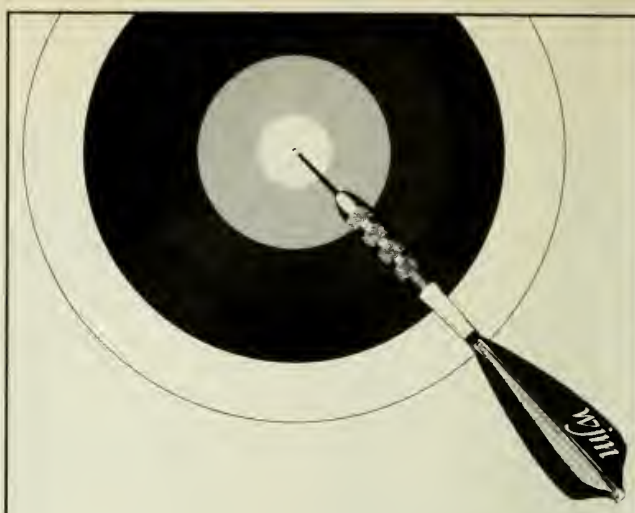

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Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

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Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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Tablets **Vaseretic** ONCE-A-DAY ACE PLUS INHIBITION

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Once-A-Day Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: ***Hypotension:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*, ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia. Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema.* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy.* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents.* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium.* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium.* See WARNINGS, *Hydrochlorothiazide*; and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide.*

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies of VASERETIC in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Enalapril Maleate: Post-marketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome: Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity, such as patent ductus arteriosus, have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk; however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Other adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Body as a Whole:* Syncope, chest pain, abdominal pain. *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia. *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Skin:* Pruritus, rash. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, decreased libido, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation, hypotension; angina pectoris. *Digestive:* Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, glossitis. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion, ataxia. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, pneumonia, bronchitis, rhinorrhea, asthma, upper respiratory infection. *Skin:* Herpes zoster, alopecia, flushing, photosensitivity. *Other:* Vasculitis, blurred vision, taste alteration. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide—Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 341B—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

MSD
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For more information, consult your MSD Representative or see Prescribing Information.
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J9VT10(305)

The Anyfingers Patch.

All nitroglycerin patches work.

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Transdermal Infusion System

Easy to open... apply... remove.

5 mg patch, actual size.

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(nitroglycerin)
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- **Easy opening—even for arthritic hands.**
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BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription.
Revised 09/87
EDP #I030160
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All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

KEY™ Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA
World leader in drug delivery systems.

ND-2142/14579303

In Memoriam

Arizona Medical Association

Clark, Clarence L., Tucson. Died May 2, 1989, aged 74. Graduate of St Louis University School of Medicine, 1940. Licensed in Arizona in 1965. Dr Clark was a member of the Pima County Medical Society.

California Medical Association

Abraham, Robert K., Los Angeles. Died Feb 23, 1989, aged 65. Graduate of Louisiana State University School of Medicine, New Orleans, 1948. Licensed in California in 1948. Dr Abraham was a member of the Los Angeles County Medical Association.

Batzle, J. Harold. Died Apr 8, 1989, aged 73. Graduate of University of Wisconsin, Madison, 1940. Dr Batzle was a member of the Riverside County Medical Association.

Beerman, Herman M., Los Angeles. Died Mar 31, 1989, aged 89. Graduate of University of Maryland School of Medicine, Baltimore, 1924. Licensed in California in 1926. Dr Beerman was a member of the Los Angeles County Medical Association.

Borsook, Mannie E., Los Angeles. Died Mar 3, 1989, aged 81. Graduate of University of Toronto Faculty of Medicine, Toronto, Ontario, 1938. Licensed in California in 1942. Dr Borsook was a member of the Los Angeles Medical Association.

Brandt, Raymond A., Santa Ana. Died Feb 19, 1989, aged 72. Graduate of University of Illinois, Chicago, 1943. Dr Brandt was a member of the Orange County Medical Association.

Bussard, Harry A., Tulare. Died Apr 1, 1989, aged 70. Graduate of University of California, Irvine, 1962. Dr Bussard was a member of the Tulare County Medical Society.

Campbell, Marian, Santa Maria. Died Apr 13, 1989, aged 76. Graduate of Women's Medical College, Philadelphia, 1947. Licensed in California in 1958. Dr Campbell was a member of the Santa Barbara County Medical Society.

Carroll, Walter W., Los Angeles. Died Feb 26, 1989, aged 73. Graduate of Northwestern University Medical School, Chicago, 1941. Licensed in California in 1951. Dr Carroll was a member of the Los Angeles County Medical Association.

Coate, Joseph D., Oakland. Died Feb 28, 1989, aged 86. Graduate of Indiana University School of Medicine, Indianapolis, 1930. Dr Coate was a member of the Alameda-Contra Costa Medical Association.

Colburn, Justin R., Oakland. Died Mar 6, 1989, aged 78. Graduate of Stanford University, 1935. Dr Colburn was a member of the Alameda-Contra Costa Medical Association.

Craig, Leela, Berkeley. Died Apr 16, 1989, aged 83. Graduate of University of California, San Francisco, 1932. Dr Craig was a member of the Alameda-Contra Costa Medical Association.

Czatt, John H., Modesto. Died Mar 13, 1989, aged 93. Graduate of Ohio State University, Columbus, 1925. Dr Czatt was a member of the Stanislaus Medical Society.

Davis, Edward H., Los Angeles. Died Mar 25, 1989, aged 61. Graduate of New York University School of Medicine, 1953. Licensed in California in 1954. Dr Davis was a member of the Los Angeles County Medical Association.

Diorio, Carmine D., San Bernardino. Died Apr 20, 1989, aged 67. Graduate of Georgetown University School of Medicine, Washington, DC, 1946. Licensed in California in 1973. Dr Diorio was a member of the San Bernardino County Medical Society.

Dobos, Joseph, San Francisco. Died Feb 2, 1989, aged 58. Dr Dobos was a member of the San Francisco Medical Society.

Douglass, Parry, San Francisco. Died Feb 6, 1989, aged 85. Dr Douglass was a member of the San Francisco Medical Society.

Evans, Harrison S. Died Jan 21, 1989, aged 77. Graduate of Loma Linda University School of Medicine, 1936. Licensed in California in 1962. Dr Evans was a member of the San Bernardino County Medical Society.

Fine, Max, San Francisco. Died Mar 29, 1989, aged 89. Dr Fine was a member of the San Francisco Medical Society.

Fritz, Samuel H., Los Angeles. Died Mar 4, 1989, aged 77. Graduate of Loma Linda University School of Medicine, 1948. Licensed in California in 1948. Dr Fritz was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

Huelsmann, Donald, Albuquerque. Died May 19, 1989, aged 72. Graduate of Washington University, St Louis. Licensed in New Mexico in 1949. Dr Huelsmann was a member of the Greater Albuquerque Medical Association.

Utah Medical Association

McMurrin, James Allen, Ogden. Died Apr 8, 1989, aged 71. Graduate of Cornell University, New York, 1943. Licensed in Utah in 1953. Dr McMurrin was a member of the Weber County Medical Society.

Noyes, Kenneth E., American Fork. Died Nov 17, 1988, aged 87. Graduate of Jefferson Medical School, Philadelphia, 1924. Licensed in Utah in 1925. Dr Noyes was a member of the Utah County Medical Association.

Squires, Russel Martin, Salt Lake City. Died Mar 22, 1989, aged 50. Graduate of University of Utah, 1965. Licensed in Utah in 1966. Dr Squires was a member of the Salt Lake County Medical Society.

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously, and are not simultaneously under consideration by any other publication.

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Revised 10/1/87

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 28-29—**Coconino County Medical Society Summer Seminar and Day of Surgery.** Little America, Flagstaff. Fri-Sat. Contact: Coconino County Medical Society, PO Box 392, Flagstaff 86002.

September 22-23—**Cancer Reviews.** Orangetree Golf Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

October 14—**Practical Management of Common Cardiovascular Problems.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 3-4—**Neuro-oncology and Stereotactics: Current Approaches to CNS Neoplasia.** Hyatt Gainey Ranch Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 9-11—**Second Annual Spine Workshop.** Camelback Inn, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix 85013.

November 18—**Gynecologic Surgery.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Mon. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

July 21-22—**American In-Vitro Allergy/Immunology Society Annual Program.** American In-Vitro Allergy/Immunology Society at San Diego Marriott Hotel and Marina. Fri-Sat. 12 hrs. $200. Contact: Betty Kahler, PO Box 459, Lake Jackson, TX 77566. (409) 297-5636.

September 21-22—**Modern Approaches to Allergy and Clinical Immunology.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. 15 hrs. $300. Contact: UCSF.

ANESTHESIOLOGY

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $100. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 22-24—**Anesthesia Practice 1989.** Anesthesiology Educational Foundation at Hyatt Regency, Monterey. Fri-Sun. 12.5 hrs. Contact: AEF, PO Box 24230, Los Angeles 90024. (213) 825-0736.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 22)

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Method of Computing the Balance for Purchases	Average Daily Balance (including new purchases)
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CONTINUING MEDICAL EDUCATION

(Continued from Page 20)

CARDIOLOGY

July 15—**Cardiology, Holter Monitoring, and Stress Testing Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sat. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

July 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Contact: Deborah Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

September 20—**Optimum Use of Diagnostic and Therapeutic Technologies in Clinical Practice.** American Heart Association Los Angeles at Beverly Hilton. Wed. 9 hrs. $120. Contact: Marlin Ledbetter, 3550 Wilshire Blvd, Ste 500, Los Angeles 90010. (213) 385-4231.

DERMATOLOGY

July 16—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sun. 7 hrs. $195. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 4-5—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll, Ste 207, Glendora 91740. (818) 963-7684.

November 2-5—**International Hot Spots in Dermatology: The Patient, the Disease, the Physician and the Art.** Kauai Academy of Continuing Education at Stouffer's Waiohai Beach Resort, Poipu, Hawaii. Thurs-Sun. Contact: David J. Elpern, MD, PO Box 457, Kalaheo, HI 96741.

EMERGENCY MEDICINE

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. Contact: UCD.

December 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. $450. Contact: UCSD.

INTERNAL MEDICINE

August 20-25—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

September 7-9—**New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, PO Box 210211, San Diego 92121. (619) 453-6222.

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

(Continued on Page 27)

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60 mg GREATER DOSAGE FLEXIBILITY 90/120 mg

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†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

1419H8

CARDIZEM® diltiazem HCl/Marion

ANTIANGINAL PROTECTION PLUS SAFETY

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BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria.
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

Rx
Cardizem® (diltiazem HCl)
☐ 60 mg ☐ 90 mg
☐ 120 mg
Sig: tid

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, W B Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlop S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Horo MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559.

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► ***For further information, call (213) 206-8983.***

CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. 16 hrs. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

OB/GYN

July 29-August 8—**Update in Urogynecology.** UCI at Hawaii. 1 week/2 days. Contact: UCI.

October 12-13—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott Hotel, Newport Beach. Thurs-Fri. Contact: UCI.

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

OPHTHALMOLOGY

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

September 15-16—**Uveitis Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Quail Lodge, Carmel Valley. Fri-Sat. Contact: UCSF.

PEDIATRICS

July 18—**22nd Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel Nob Hill, San Francisco. Thurs-Sat. 16 hrs. $275. Contact: UCSF.

July 21-22—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

August 11-13—**2nd Annual Postgraduate Course.** UCI at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: UCI.

October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

(Continued on Page 30)

David S. Gullion, M.D., CAP/MPT member, is board certified in Medical Oncology and Hematology. He is in private practice specializing in Oncology. An Associate Clinical Professor of Medicine at a leading university, Dr. Gullion conducts research in continuing medical education.

LIKE DAVID S. GULLION, M.D. CAP/MPT MEMBER SINCE 1985.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 27)

PSYCHIATRY

July 29—**Violent Innocence: Denial as an Object Relation.** Continuing Education Seminars at Los Angeles. Sat. 6 hrs. $95. Contact: Continuing Education Seminars, (213) 475-8300.

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

RADIOLOGY

July 27-30—**3rd Annual Symposium on Magnetic Resonance Imaging.** Ritz-Carleton Resort Hotel, Laguna Niguel. Thurs-Sun. 23 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 29—**Abdominal Imaging Conference.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

July 30-August 3—**Napa Valley Imaging Update: MRI 1989.** UCD at Silverado Country Club, Napa Valley. Sun-Thurs. 17 hrs. $435. Contact: Nina Musselman, (916) 453-5390.

July 31-August 4—**Modern Radiology Practice.** UCSD at Four Seasons Biltmore Hotel, Santa Barbara. Mon-Fri. 24 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 24-27—**Physics and Biology of Radiology.** UCSD at Town & Country Hotel, San Diego. Thurs-Sun. 25 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 7-10—**5th Annual Sonography Update for Physicians and Sonographers.** UCSD at San Diego Marriott Hotel and Marina. Thurs-Sun. 18 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 23-24—**Weekend MRI Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Sat-Sun. 12 hrs. $195. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

October 2-5—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center and University of Cincinnati College of Medicine at Ritz-Carlton Hotel, Laguna Niguel. Mon-Thurs. 18 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 7-8—**Ultrasound Update: 1989.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. Contact: UCD.

October 12-14—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center Cincinnati at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sat. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

July-December—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

July 19-22—**5th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic and Research Foundation at La Jolla. Wed-Sat. 25 hrs. $799. Contact: Judy Plis, Scripps Clinic, La Jolla 92037. (619) 554-8646.

August 5-12—**Fine Needle Biopsy Course.** UCSF at Westin Hotel, Kauai, Hawaii. 1 week. 25 hrs. $895. Contact: UCSF.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

September 15—**Ultrasonic Liver Surgery.** UCD at Davis. Fri. 8 hrs. $250. Contact: UCD.

October 11-14—**Hip and Knee Reconstructive Surgery 1989.** UCLA at Sheraton Kauai Hotel Poipu Beach, Kauai, Hawaii. Wed-Sat. Contact: UCLA. (213) 825-5840.

OF INTEREST TO ALL PHYSICIANS

July 24-28—**Sports Medicine 1989: A Practical Approach to Caring for Today's Athlete.** UCSD at The Princess Hotel, San Diego. Mon-Fri. 22 hrs. $335. Contact: UCSD.

July 31-August 3—**Practical Orthopaedic Sports Medicine.** Children's Hospital Oakland at Hyatt Regency, Waikoloa, Kona Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Stuart Zeman, MD, 2999 Regent St, No 203, Berkeley 94705. (415) 540-8686.

August 2-6—**Wilderness Medicine: '89.** American College of Emergency Physicians California Chapter at Squaw Valley, Lake Tahoe. Wed.-Sun. 22 hrs. $395. Contact: Jackie Silva, MD, PO Box 321, Yreka 96097. (916) 842-4667.

August 11-12—**Office Practice Enhancement: Non-invasive Diagnostic Testing.** Medical Education Collaborative at Lake Tahoe, Nevada. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

August 11-13—**Chemical Dependency Treatment and Recovery for the 90s.** UCLA at Ackerman Union. Fri-Sun. 15 hrs. $190. Contact: UCLA.

August 25-27—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 19 hrs. $235. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

September 23—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Scripps Amphitheater. Sat. 6 hrs. $50. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

October 9-13—**Selected Topics in Sports Medicine in Conjunction With the Ironman Triathlon World Championship.** Tropical Seminars at Kona Surf Resort, Kailua-Kona, Hawaii. Contact: Robert Bethel, DO, PO Box 1399, Poulsbo, WA 98370. (206) 697-5776.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 30)

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas Hilton. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

IDAHO

July 27-29—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701.

August 7-8—**Northwest Regional Perinatal Conference—Current Issues in OB/GYN, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Mon-Tues. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 17-20—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Contact: Anne Woodrow, NM Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 20-22—**General Surgical Postgraduate Course.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 7-9—**Concepts and Controversies in Perinatal Care.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 9-10—**First American Cancer Society Interdisciplinary Cancer Conference.** Bishop's Lodge, Santa Fe. Contact: Stephanie Gooch, American Cancer Society, NM Chapter, 5800 Lomas NE, Albuquerque 87110. (505) 262-2336.

September 15-16—**Essentials of Health Care for the Elderly.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 15-16—**New Mexico Chapter, American College of Surgeons—Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: NM Chapter, ACS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

September 22-23—**Southwestern Psychiatric Symposium on Schizophrenia and Depression.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

October 12-14—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

(Continued on Page 32)

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For more information, call 1-800-ACS-2345.

AMERICAN CANCER SOCIETY®

(Continued from Page 31)

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

July 16-21—**Seventh Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Jackson Hole, Wyoming. Contact: Midge Beckman, (801) 581-7480.

July 17—**Seventh Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon. Jackson Hole, Wyoming. Contact: Midge Beckman, (801) 581-7480.

July 20—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

September 21-23—**Utah Perinatal Association** (Sponsor: UUMC). Thurs-Sat. University Park Hotel, Salt Lake City. Contact: Raine Beach, (801) 581-2598.

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

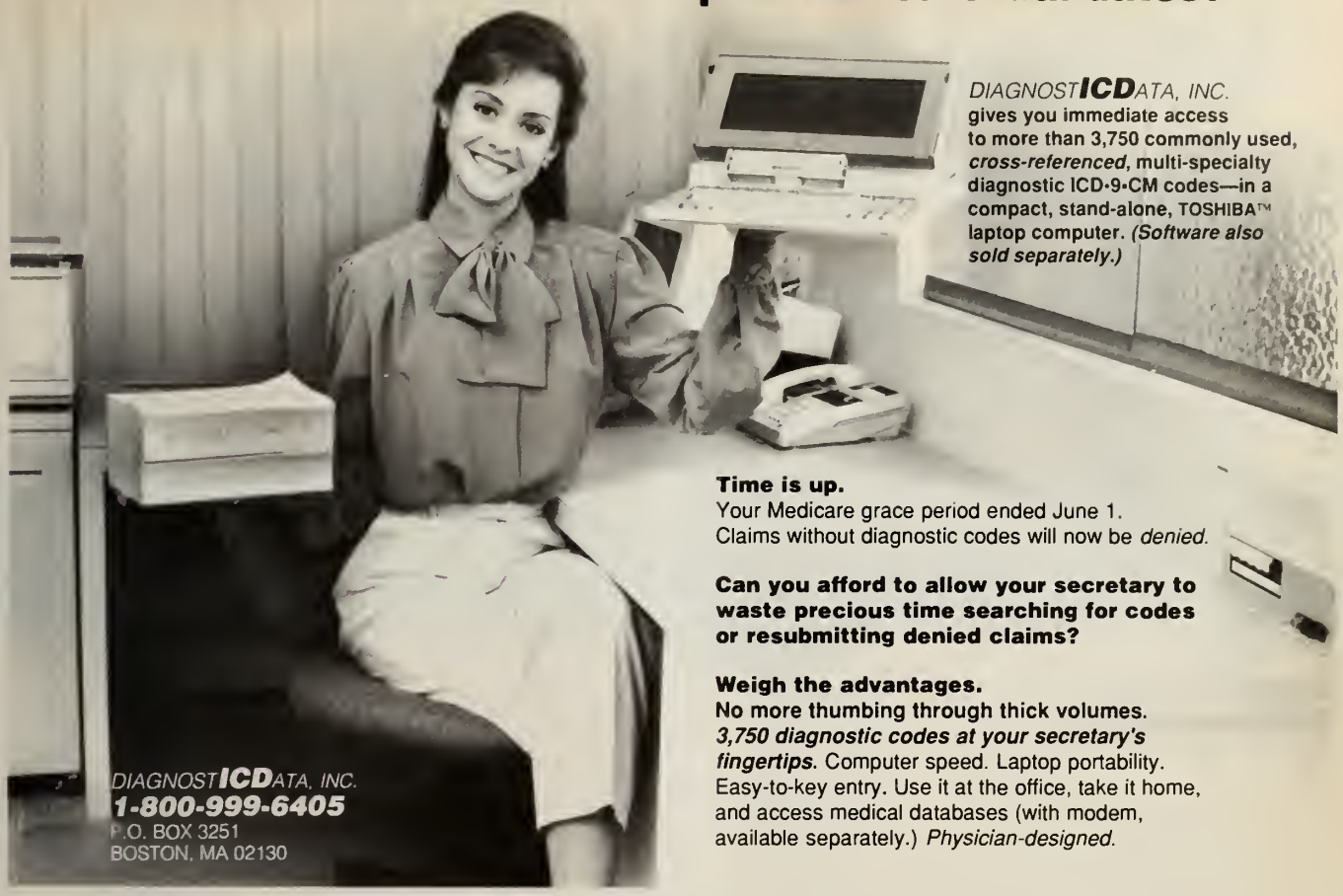
WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

(Continued on Page 33)

Can Your Office Measure Up to Medicare Mandates?



CONTINUING MEDICAL EDUCATION

(Continued from Page 32)

July 28—**Expert Witnesses and Medical Malpractice.** Seattle. Fri. Contact: U/W.

August 7-12—**Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 12—**Instrumented Measurement of A/P Knee Laxity.** Seattle. Sat. Contact: VMMC.

September 7-9—**Annual Review of Neurology and Neurosurgery.** Seattle. Thurs-Sat. Contact: U/W.

September 11-15—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 15-16—**Allergy Update.** Seattle. Fri-Sat. Contact: U/W.

September 15-16—**Urology Update.** Seattle. Fri-Sat. Contact: VMMC.

October 6—**23rd Annual Cancer Conference: Innovative Management of Cancer Patients.** Seattle. Fri. Contact: VMMC.

October 12-14—**Internal Medicine Review.** Seattle. Thurs-Sat. Contact: U/W.

October 27-28—**Sinus Surgery.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

October 27-28—**Acid-Peptic Disease: New Perspectives.** Seattle. Fri-Sat. Contact: VMMC.

November 3—**The Injured Knee: Diagnosis, Treatment, and Therapy.** Seattle. Fri. Contact: VMMC.

November 3-4—**Medical Updates—School of Medicine.** Seattle. Fri-Sat. Contact: U/W.

November 10—**Sexual Abuse in Medical Practice.** Location to be announced. Fri. Contact: U/W.

November 10—**Outpatient Treatment of Infections: Oral Antibiotic Therapy.** Seattle. Fri. Contact: VMMC.

November 16-17—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 29-December 1—**Update on Surgery.** Seattle. Wed-Fri. Contact: U/W.

December 1—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** Sun Valley. Fri-Sun. Contact: U/W.

WYOMING

July 17-21—**Seventh Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Sun-Fri. Contact: Midge Beckman, (801) 581-7480.

October 6—**Update on Infectious Diseases.** West Park Hospital, Cody. Fri. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody 82414. (307) 527-7501, ext 250.

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526. ◆

Millions of Americans are being asked to look out below

The GSE™: What it means to you

Across the country, sexually active adults will soon be encouraged to do a special health check called a GSE... a genital self-examination. A simple examination to check for potential signs of a sexually transmitted disease (STD).

The GSE is the heart of a nationwide campaign to heighten public awareness of STDs. This program is sponsored by Burroughs Wellcome Co. in conjunction with major medical associations.*

Sexually active adults will be urged to send for a free guide that explains how to perform a GSE. The guide discourages self-diagnosis and encourages seeing a physician if anything suspect is found.

As the GSE campaign gains momentum, you may be seeing more patients coming to your office with concerns about sexually transmitted diseases. While STDs are currently regaining their foothold on the American population, the GSE program offers a promising outlook for reducing their spread.

* The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, and the American Osteopathic Association.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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April 1989 ZO-970

GENITAL
SELF-EXAMINATION
TM

GSE GUIDE

What is a GSE™?

GSE stands for genital self-examination. It's a simple examination that you can give yourself to see if you have any of the signs or symptoms that might indicate the presence of a sexually transmitted disease (STD). This GSE Guide will explain how to give yourself a genital examination, including the parts of your body to look at, and the signs and symptoms to look for. **Do not try to make a diagnosis yourself.** What you find may or may not be a sign of a sexually transmitted disease. Many conditions have similar appearances. Only a physician can make a proper diagnosis.

Anyone who has sexual relations is potentially at risk for contracting a sexually transmitted disease. The more sexual partners you have, the greater your risk. If you're sexually active, read this GSE Guide carefully. If you are currently monogamous (having sex with only one person), but were not monogamous in the past, you may want to give yourself a GSE because some STDs remain undetected for years. For the same reason, if you are presently not involved in a sexual relationship, but had several sexual partners in the past, you should also consider giving yourself a GSE. The next section will tell you why a GSE is so important to you and those you care about.

Sponsored by Burroughs Wellcome Co. in conjunction with the American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, and the American Osteopathic Association.

Why is a GSE™ important?

A genital self-examination is important because it may help you discover if you have any of the signs or symptoms that might indicate the presence of a sexually transmitted disease. More than 10 million men and women from all walks of life are affected by STDs each year. And many people who have a sexually transmitted disease don't know they have one.

It is impossible to know if you have a sexually transmitted disease without knowing the telltale signs. Many STDs have symptoms that may be confused with one another and with other diseases. Some STDs have symptoms that appear and then disappear. However, just because the signs and symptoms disappear doesn't mean the disease has disappeared. You could still be passing on a sexually transmitted disease to someone you care about without realizing it.

Additionally, by helping you find out if you have a sexually transmitted disease, a GSE may help prevent further complications. Left untreated, some STDs can cause serious health problems, including infertility, heart disease, or brain damage. Some STDs may also be passed from a mother to her baby before or during birth.

STDs are serious...but fortunately treatment programs are available for most STDs. The earlier you detect symptoms, seek diagnosis, and begin a treatment program, the less likely that the disease will cause you physical harm, or be spread to others.

The following section will describe how to give yourself a genital self-examination. Please note that there are separate sections for men and women.

How do I give myself a GSE™? (for men)

Before you begin a genital self-examination, it is important to understand the words that describe the genital portion of your body. The top or head of your penis contains the urinary opening (urethra). The head may be covered with foreskin if you are not circumcised. Moving down past the head is the shaft of your penis. The very bottom of the shaft is called the base. The base of the penis is the area where your pubic hair begins. The underside of the penis refers to the side you can't see when looking down. Underneath your penis is the scrotum, a sac enclosing the testicles, which hangs slightly away from your body.

Now that we've described your genital area, let's begin your genital self-examination. Once undressed, hold your penis in your hand. Start by examining the head of the penis from the urinary opening down to where it extends out a little just above the shaft. If you are not circumcised, pull down the foreskin to examine the head. Look over the entire head of the penis in a clockwise motion. Carefully look for any bumps, sores, or blisters on the skin. Sometimes the bumps or blisters may be red; at other times they may be light-colored. They may even look like pimples. Bumps and blisters sometimes develop into open sores. If you see anything that resembles a sore, blister, or bump, see your physician.

In addition, look for warts. Genital warts may look like warts you may have seen on other parts of your body. They may first appear as very small, bumpy spots. Left untreated, they could develop a fleshy, cauliflower-like appearance. Some warts are hard to detect with the naked eye. If you feel any bumpy growth, no matter how slight, have it checked by a physician.

Once you've examined the head of the penis, move down the shaft and look for the same signs or symptoms. Then go on to the base. At the base, try to separate your pubic hair with your fingers so you can get a good look at the skin underneath. After careful examination here, move on to the underside of the penis. This area is often difficult to see, and sometimes gets overlooked. It is very important that you check this part of your body. You may want to use a mirror to be sure that you've

seen the entire underside. The mirror may also be helpful as you move on to the scrotum. Handling each testicle gently, examine the scrotum for the same signs or symptoms. Also, be alert to any lump, swelling, or soreness in the testicle.

Once you've examined your entire genital area for redness, sores, bumps, and warts, be aware of these other symptoms often associated with sexually transmitted diseases. STDs may cause burning or pain when you urinate. Some STDs cause a drip or discharge from the penis. This drip may vary in both color and consistency. The drip could be thick and yellow, or it could be watery or very slight.

If you notice any of the signs or symptoms described—no matter how slight—see your physician. In addition, if you feel you may have come in contact with someone who has a sexually transmitted disease, consult your doctor even if you discover no signs or symptoms during your genital self-examination. You may or may not have a sexually transmitted disease. The only way to know for sure is to see your physician for a diagnosis.

Please be aware that the symptoms of some STDs are sometimes so mild you might not notice them, or the symptoms might seem to disappear; however, you are still infected and could spread disease to others. Symptoms of STDs may not appear for weeks, even months after the sexual encounter. So if you're sexually active, be sure to see your physician and get an examination on a regular basis. Between physician check-ups, use the GSE periodically to check yourself for early warning signs. If you suspect anything, don't wait. See your physician.

How do I give myself a GSE™? (for women)

Before starting your genital self-examination, it is important to understand the words that describe the genital portion of your body. Let's start where your pubic hair begins and move down. Your pubic hair above your vagina grows from soft fatty tissue called the mons. Your pubic hair continues down between your legs in a fleshy area that forms flaps called the outer lips or labia. The outer lips surround soft flaps of skin that are hairless. These are the inner lips. At the top of your inner lips (right below the mons), you'll find your clitoris. The clitoris is covered by a soft fold of skin, called the hood of the clitoris. If you pull the hood up, you will see the clitoris. Notice that the inner lips are attached to the underside of the clitoris. Right below this attachment you will see the urinary opening. Below that is a larger opening called the vaginal opening.

Now that we've described your genital area, let's begin your genital self-examination. Once undressed, start by examining the area that your pubic hair covers from the mons down to the area between your legs. You may want to use a mirror and position it so that you can see your entire genital area. Even with a mirror, you may find it difficult to see the area from your urinary opening down. Do the best you can without putting yourself in an uncomfortable position.

Start by spreading your pubic hair apart with your fingers. Carefully look for any bumps, sores, or blisters on the skin. Sometimes the bumps or blisters may be red, at other times they may be light-colored. They may even look like pimples. Bumps and blisters sometimes develop into open sores. If you see anything that resembles a sore, blister, or bump, see your physician.

In addition, look for warts. Genital warts may look like warts you may have seen on other parts of your body. They may first appear as very small bumpy spots. Left untreated, they could develop a fleshy, cauliflower-like appearance. Some warts are hard to detect with the naked eye. If you feel any bumpy growth, no matter how slight, have it checked by a physician.

Once you've examined the area covered by pubic hair (the mons and the outer lips), spread

your outer vaginal lips apart and take a close look at the hood of your clitoris. Then gently pull the hood up to reveal your clitoris. Once again, look for any bumps, blisters, sores, or warts.

Next look at both sides of your inner lips for the same signs. Then move on to examine the area around your urinary opening and your vaginal opening. This is as far as we recommend that you look. Some signs of STDs may appear up in your vagina, near your cervix, and out of view. Therefore, if you feel you may have come in contact with someone who has a sexually transmitted disease, see your physician even if you discover no signs or symptoms during your genital self-examination.

In addition to examining your entire genital area for redness, sores, blisters, bumps, or warts, be alert to other symptoms that are often associated with STDs. Some STDs may cause a vaginal discharge. Because most women have a vaginal discharge from time to time, try to be more aware of what your "normal" discharge looks like. Discharge caused by a sexually transmitted disease will appear more unusual—it may be thicker, possibly yellow. It may also have an odor. Other symptoms or signs to be aware of include a painful or burning sensation when urinating, pain in your pelvic area, bleeding between menstrual periods, or an itchy rash around the vagina.

If you notice any of the signs or symptoms described—no matter how slight—see your physician. You may or may not have a sexually transmitted disease. The only way to know for sure is to see your physician for a diagnosis. Please be aware that the symptoms of STDs are sometimes so mild that you might not notice them, or the symptoms might seem to disappear; however, you are still infected and could spread disease to others. Symptoms of STDs may not appear for weeks, or even months after the sexual encounter. So if you're sexually active, be sure to see your physician and get an examination on a regular basis. Between physician check-ups, use the GSE periodically to check yourself for early warning signs. If you suspect anything, don't wait. See your physician.

What are the signs and symptoms of the more common sexually transmitted diseases?

There are as many as 20 different STDs. This section presents some of the signs and symptoms of the more common STDs, many of which have recently been on the rise. **Do not attempt to make a diagnosis based on this information. So many different STDs have similar symptoms or appearances that only a physician can make an accurate diagnosis.**

Chlamydia (Klah-MID-ee-uh)

Chlamydia is the most common STD in the US today, with as many as 4 million new cases occurring each year. Chlamydia affects both men and women. Symptoms are often mild and therefore frequently go unnoticed. If symptoms do appear, they usually occur within 1 to 3 weeks after sex with an infected partner.

Women may experience pain while urinating, a vaginal discharge, or abdominal pain. Left untreated, chlamydia may lead to a serious infection called pelvic inflammatory disease (PID). Approximately 100,000 women each year become infertile as a result of PID. In men, chlamydial infections can cause a discharge from the penis, or pain when urinating. Men may also see a little crusting at the tip of the penis.

Genital Herpes (JEN-a-tul HER-peez)

Genital herpes currently affects an estimated 30 million Americans—men and women alike. As many as 500,000 new cases are expected to occur each year. Symptoms of a first episode usually appear within 2 to 10 days after sex with an infected partner. Early symptoms may include a burning sensation or pain while urinating, pain in the buttocks, legs, or genital area, vaginal discharge, or a feeling of pressure in the pelvic area. In a few days, small red bumps appear in the genital area. Later these bumps develop into painful blisters, which eventually open up, then crust over and heal.

Even after the sores disappear, the herpes virus remains in the body. The virus can reactivate at any time and cause an outbreak of new sores. Some people get a warning as to when the outbreak will occur. They may feel a tingling sensation in the genital area before sores appear. The frequency and severity of genital herpes outbreaks vary from person to person, and may range from none to monthly outbreaks. The herpes virus may also be passed on to an infant during childbirth—causing serious infection.

Gonorrhea (GON-oh-REE-ah)

Gonorrhea is reported to affect an estimated 1 million people each year. It is believed that another 1 million cases go unreported each year. This disease affects both men and women.

Symptoms usually occur within 2 to 10 days after sex with an infected partner. Often, those who are infected show no signs. Women may experience pain or burning when urinating or a yellowish vaginal discharge. Advanced symptoms include bleeding between menstrual periods, swollen joints, fever, or pain in the pelvic area. In men, symptoms of gonorrhea include burning when urinating, and a discharge from the penis.

Untreated gonorrhea can lead to pelvic inflammatory disease (PID) in females, frequently resulting in sterility. It may also cause arthritis and, in rare cases, heart disease. Women infected with gonorrhea can also pass the disease on to an infant during delivery—causing serious infection and possible blindness.

Genital Warts (JEN-a-tul WORTS)

Genital warts affect at least 3 million American men and women each year. Often this sexually transmitted disease does not cause noticeable symptoms. Signs include small bumpy warts on or near the sex organs, usually developing 3 weeks to 3 months after sex with an infected partner. In women, they sometimes occur inside the vagina, out of sight. They may appear on the lips of the vagina or around the anus. In men, they usually appear on the penis. However, they are sometimes found on the scrotum or around the anus.

These warts, caused by a group of sexually transmitted viruses, can occasionally grow into large

masses that are hard to clear up. A mother with warts may pass them on to her baby during childbirth. Some genital warts have also recently been associated with certain types of cancer.

Syphilis (SIF-uh-liss)

After years of being on the decline, syphilis is reported to be on the rise again. In 1986, syphilis was reported to affect 70,000 Americans and that number is growing.

This sexually transmitted disease goes through several stages and early symptoms are often mild. The first symptom, usually occurring 1 to 12 weeks after sex, is usually a painless sore on the genitals, called a chancre (SHANK-er). It may occur inside the body and go unnoticed. The sore disappears within a few weeks, but the disease progresses.

In the second stage of the disease, anywhere from 2 to 12 weeks after the sore disappears, a skin rash usually surfaces. It may appear on a few areas of the body, or it may cover the body; you may also get flu-like symptoms. The rash and flu-like symptoms eventually go away, but you still have syphilis. Left untreated, syphilis can lead to blindness, heart disease, brain damage, and even death.

How can I reduce my chances of contracting a sexually transmitted disease?

Naturally, the best way to reduce your risk of contracting a sexually transmitted disease is by not having sex. You can also reduce your risk by having sex with one mutually faithful uninfected partner, or by using a condom during sex. Remember, the more sexual partners you have, the greater your risk. You should also learn to recognize the signs of common sexually transmitted diseases.

As you are probably aware, the most serious sexually transmitted disease today is human immunodeficiency virus (HIV) infection, which may result in acquired immunodeficiency syndrome (AIDS). You can reduce your risk of contracting the AIDS

virus by following the advice mentioned above. You can also reduce your risk by not having sex with someone who shoots drugs or engages in anal sex, and by not engaging in vaginal, oral, or anal sex with an infected person.

If you think you may have been infected with AIDS or any other sexually transmitted disease, see your physician immediately.

Can sexually transmitted diseases be treated?

When diagnosed early, and attended to promptly, almost all STDs can be treated. If you think you may have contracted a sexually transmitted disease, see your physician immediately. If you are or have been sexually active with someone other than a long-term monogamous partner, get a genital examination by a physician on a regular basis. Be honest and open with your doctor about your sexual history, including any risky behavior you may have engaged in. In between physician check-ups, give yourself a genital self-examination. If you have already been treated and you still have symptoms, see your physician. Sometimes more than one infection is present. In other cases, it suggests that your partner is also infected and needs treatment.

Remember, most STDs can be treated. The sooner you spot symptoms, seek a diagnosis and get treatment, the less likely the disease will cause you harm. And you'll also be preventing the disease from spreading to and hurting someone you care about.

Presented as a public service by Burroughs Wellcome Co
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the American Academy of Family Physicians,

the American College of General Practitioners
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THE FRANCIS A. COUNTWAY
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JUL 18 1989

Medical Malpractice: It Is Society's Problem, Not Only Ours

Marshall B. Block, M.D.

As physicians we take risks. In our present climate, we alone share the burden for having an adverse outcome in a patient encounter. An adverse outcome may be due to negligence or just a poor result. The question that I would like to ask is whether this is fair?

The making of a physician is not a simple task. A definitive end point, "He is a *good* doctor!" cannot be easily determined, although attempts have been undertaken vis-a-vis the national boards of medical examiners, state licensing boards and American boards of specialty care. The public perceives this diversity whenever they ask "I want to see the BEST one" when a referral is needed. Whether someone is a competent physician depends on many variables which no doubt is responsible for the difficulty in producing a uniform product. The twenty or so odd years prior to entering medical school is the foundation upon which medical education is grounded. The influences during these early years are thought by some to be more important in an individual's ultimate outcome than anything which occurs afterwards. Genetics, the effect of the home environment, peer pressure and schooling all produce the product that is chosen by the Medical School Admissions Committee. Because mankind is so diverse, it is obviously difficult to be certain of our choices. Adding to this complexity is medical school's intense competitive training. This results in a situation where the chances for "failure" are magnified. It is amazing considering the "unscientific" method that has been utilized, that we turn out so many reasonable physicians.

Once turned loose, the physician is faced with a host of influences, medical and others, which flavor his response to varying clinical situations. Two of the most important are the physician-patient interaction and the physician-information challenge. A new one will be the physician-economic interaction.

Much has previously been written about the patient-physician encounter. The most important, I think, is that today society perceives physicians as having the ability to give them the "final answer." This is translated by the patient to mean that physicians have solutions for all of their medical problems and if they fail to help them, there is something wrong with the physician's skills.

Implicit in the above perception is society's conception of our supposedly "solid" information base. How firm are the facts on which we base our decisions? In the office we don't have time for the Null hypothesis, "p" values or random doubled blind studies. Rather, we must distill all that is known for a patient and come to a decision which can have far reaching implications. The magnitude of the quicksand upon which we practice is evidenced by the oppressive number of journal articles which appear weekly, bi-weekly, monthly and quarterly throughout the world's literature. It is little wonder then that the text books we buy are outdated before we can read them. If the sand is changing so rapidly, it is impossible to be certain of much one day, knowing that tomorrow it may be different. Yet, society considers medical knowledge unshakable, similar to that in the Physical Sciences. Unfortunately, there is little in medicine which is static and this places an undue burden on us, its practitioners.

The revolution in financing of health care is resulting in dramatic changes in its delivery. For instance, the previously harmonious physician-hospital relationship has changed. Hospitals no longer see physicians as independent providers of patients to fill their beds. Rather, hospitals feel that if they are to survive they must control physicians in order to limit their ordering capacity and to be able to market their services. In addition, payments to physicians are coming under increasing scrutiny. "Less" is now better than "more" according to employers, employees and insurance carries. This is a far cry from the past, where patients used to say "Find out what is wrong with me, no matter what it costs!"

The physician-patient relationship has changed dramatically in this environment. Patients choose doctors not because of their skills but because they are on a "list." Patients' allegiance to physicians is rapidly disappearing as employer groups change plans yearly. We have all seen patients who enter a new relationship because it would cost them less than to continue to see their physician of twenty years. Medical records also are no longer sacrosanct. Patients sign off when entering plans allowing their

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In This Issue:

- The Problem That Won't Go Away
- Dean's Editorial
- Computer Laser Hip Replacement
- Physicians in the News
- New Members
- Classified Ads

From Our President

Mark Ivey, Jr., M.D.

The structure of medicine has evolved from leeches, politics, herbs, theories, science, surgery and often times, from prayers. Over the years it has developed the capacity to provide injured and sick people with compassionate and comprehensive care of astonishing technological sophistication.

Yet it's no secret that people are not happy. Patients are not happy. Physicians are not happy.

What has happened to our profession? Somehow the parts have started to stick and have stopped functioning very well.

Patients are tired of exorbitant health care costs, sickened by their inability to buy adequate, affordable health care insurance, and fed up with insurance bureaucracies that promise but often fail to pay for illness.

Patients are angry when they can't see physicians of their choice because of corporate patient shuffling.

Patients can't understand how a clerk in another state can deny a hospital admission that they and their own doctors know they need.

Patients are outraged by enormous legal fees and their effect on health care availability.

Patients are shocked that most of rural Arizona lacks adequate obstetrical service and are stunned by the state's policy on prenatal and perinatal care: we won't pay pennies for prenatal care but we'll willingly pay hundreds of thousands for the results of no care.

Patients are for quality, timely and improving health care; they want to be involved in their health care decisions.

And we agree. All these frustrations our patients feel and all these things they want are the outrages we feel and the ideals we strive toward.

But the integrity of our profession, its viability and its unparalleled service mission are threatened by:

- Our own inaction
- A misperceived self-indulgent image
- Pro-active non-medical organizations
- Our own political hibernation
- Third party payor chameleons who blend their image into myriads of health care delivery contracts whose verbiage conforms to the environment and
- Hospital administrators who give lip service to patient care and quality while secretly scheming to base bottom line budgets on economics.

Most of all, we are threatened by failure to adhere to a basic premise that says THE PATIENT COMES FIRST.

Continued on page 14

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Dick Pearson

THE PROBLEM
That Won't Go Away

As husband and wife, you have worked hard to reach your economic goals. You've built an estate that can provide future generations with a strong financial footing. The only problem is estate taxation. It can eliminate much of your estate's value, leaving your heirs with far less than you planned.

In 1981, Congress gave you the unlimited marital deduction and you thought your estate tax problem went away, but it didn't. THE PROBLEM was merely postponed.

The unlimited marital deduction established by the Economic Recovery Tax Act of 1981 (ERTA) places the estate tax burden on the survivors of the second spouse to die. Following the second death, however, taxes are due--shifting the burden to your children, grandchildren, or other heirs.

Several of the major life insurance companies ArMA Membership Benefits work with, have developed policies which address this situation. They are commonly referred to as "last to die" or "survivorship whole life" contracts. They are designed primarily for estate planning situations and:

- Insure two lives under one policy,
- Allow for TAX FREE accumulation of guaranteed cash values,
- Provide death benefits at the second death to ensure the liquidity needed to preserve your estate.
- Provide for a lower policy premium than for either life alone.

PAY IT NOW, OR PAY IT LATER

Compare. If you do nothing today to solve your estate tax problem it could cost you a great deal—all due in one lump sum.

If the taxable estate of the last spouse to die is:	The Tentative Federal Estate* Tax will be:	Marginal Tax Rate
$ 750,000	$ 55,500	39%
1,000,000	153,000	41
1,250,000	255,500	43
1,500,000	363,000	45
2,000,000	588,000	49
2,500,000	833,000	53
3,000,000	1,098,000	55
3,500,000	1,373,000	55
4,000,000	1,648,000	55
4,500,000	1,923,000	55
5,000,000	2,198,000	55
6,000,000	2,748,000	55
7,000,000	3,298,000	55
8,000,000	3,848,000	55
9,000,000	4,398,000	55
10,000,000	4,948,000	55

*The tentative federal estate taxes illustrated above have been computed based on the following assumptions:
- No tax is paid when the first spouse dies. The full tax is paid at the death of the surviving spouse.
- The tax has been reduced by the amount of the Unified Credit ($192,800). If the Unified Credit has been partially or completely used, the taxes will be higher.
- The expenses of probate, administration, executor's and attorney's fees and other costs are excluded in determining the taxable estate.

Continued on Page 13

ArMA Financial Services, Inc.
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See how tax-free income adds up for you

A sensible financial plan is one that eliminates taxes on your investment income--rather than just deferring taxes to a future time.

The equivalent yield table below illustrates the benefits of double tax exemption for individuals under 1988 federal tax rates and under current state tax rates. Locate your income tax bracket (after deductions and exemptions) and read across to see the approximate taxable yield needed to match the tax-free return of a **NUVEEN ARIZONA TRUST.**

For example, with joint taxable income of $29,800 to $71,900, you would be in the 32% combined federal and Arizona tax bracket and would need a taxable investment paying 10.66% to equal a tax-free return of 7.25%.

1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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Reinvestment Options You can reinvest interest and principal or principal distributions only. Then, select either a tax-free money market fund or municipal bond fund. There's no charge to reinvest, and you receive quarterly reinvestment statements.

Convenience All the work of owning municipal bonds is done for you: safekeeping of securities; watching for called bonds; collecting a semiannual interest from issuers. And, receive a year-end accounting, too.

Total Dollar or Unit Purchase You may order the number of units you wish to purchase or a dollar amount you wish to invest. The minimum investment is $5,000 or 50 units, whichever is less.

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Benzodiazepines, Anxiety, and Chloride Channels

While it is common for individuals to experience periods of anxiety during their lives, chronic anxiety is an unusual condition that is highly debilitating. Human anxiety disorders are characterized by symptoms of muscular tension, autonomic hyperactivity, apprehensive expectation and increased vigilance.[1] Thus, human anxiety has components which can be characterized as being emotional and physical.

Ethanol has anxiolytic activity and it is likely that some of the consumption of alcoholic beverages is due to this property but ethanol is not prescribed for anxiety. Some of the first drug treatments for anxiety included the use of barbiturates and propanediol carbamates (e.g. meprobamate). However, the sedative activity and low therapeutic index of these drugs limits their utility for the treatment of this disorder.

The synthesis of different benzodiazepine compounds by Leo Sternbach in the mid 1950s and subsequent introduction of chlordiazepoxide (Librium) and diazepam (Valium) in the 1960s profoundly altered the treatment of anxiety. The limited side effects and large therapeutic index of these drugs led to their widespread use for the treatment of anxiety disorders and by the 1970s they were probably the most prescribed drugs in the United States.[2]

The first information regarding the mechanism through which benzodiazepine drugs produced their effects was obtained by Schmidt et al.[3] who observed a benzodiazepine-induced increase in the dorsal root potential measured in the spinal cord after sensory nerve stimulation. Subsequent studies[4] revealed that this effect was due to the enhancement of GABA-induced chloride conductance. The glutamic acid metabolite, y-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter in the central nervous system and acts on several different types of GABA receptors. These include $GABA_A$ receptors which are associated with a chloride channel. The inhibitory effect produced by GABA at the $GABA_A$ receptor results from the opening of the ion channel and subsequent hyperpolarization of the neuronal membrane by an influx of chloride ions.

Purification of the $GABA_A$ receptor led to the identification of two protein subunits (a and B). It was proposed that the recognition or binding sites for GABA and benzodiazepines were on the B and a subunits, respectively. Genes encoding the a and B subunits have been cloned and expressed in cultured cells normally lacking $GABA_A$ receptors.[5] Cells transformed to express both subunits are hyperpolarized by GABA, but surprisingly, so are cells which express only a or B subunits. Furthermore, no combination of a or B subunits resulted in either benzodiazepine radioligand binding or modulation of GABA activity. These observations suggest that the benzodiazepine recognition site must be part of a third $GABA_A$ receptor subunit (Y).

The polymeric complex that includes the $GABA_A$ recognition site and the chloride channel is sometimes referred to as the $GABA_A$-receptor chloride-ionophore complex due to its two major constituents. In addition, the complex contains recognition sites for benzodiazepines, barbiturates, and chloride ion channel blockers (e.g. picrotoxin). Only GABA mimetic agonists and certain barbiturates appear to directly open the chloride channel. Other drugs, including benzodiazepines, barbiturates, and ethanol act to modulate the effects of GABA.

Benzodiazepine drugs produce a bipolar spectrum of pharmacological activity.[6] The familiar benzodiazepine agonists like diazepam produce anxiolytic and anticonvulsant effects at low doses while higher doses produce sedative and muscle relaxant effects. In contrast, certain benzodiazepine derivatives such as Ro 19-4603 produce anxiogenic and convulsant effects. These derivatives are referred to as inverse agonists. Between these poles lie benzodiazepine antagonists like flumazenil which have little or no biological activity but can block the effects produced by both benzodiazepine agonists and inverse agonists.

This bipolar spectrum of benzodiazepine activity is clearly evident in biochemical assays which measure chloride uptake into membrane vesicles prepared from brain tissue using 36CI- as a radioactive tracer.[7] Neither benzodiazepine agonists or inverse agonists produce changes in chloride uptake in the absence of GABA. Benzodiazepine agonists increase the rate of GABA-stimulated chloride conductance while benzodiazepine inverse agonists decrease the rate of GABA-stimulated chloride conductance. Benzodiazepine antagonists block the effects of both benzodiazepine agonists and inverse agonists without affecting the GABA-stimulated chloride conductance rate. The increase in GABA-stimulated chloride conductance produced by benzodiazepine agonists

results from an increase in the frequency of chloride channel opening. Benzodiazepine inverse agonists act to reduce this frequency.

The enhancement of GABA-stimulated chloride conductance appears to be a common mode of action for anxiolytic agents. Both barbiturates and ethanol act to enhance GABA-stimulated chloride conductance, though by somewhat different mechanisms. For example, barbiturates can directly increase chloride conductance and act to increase the duration of GABA-stimulated chloride channel opening. The ability of benzodiazepine inverse agonists to produce anxiogenic effects suggests that anxiety disorders may be a result of impaired $GABA_A$ receptor function. The location of this defect, whether at the GABAergic neuronal terminal or at the postsynaptic $GABA_A$ receptor itself will doubtlessly remain an important area of research in neuropharmacology in the future.

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■

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Physicians in the News

New ArMA President

1989-90 ArMA President Mark Ivey, Jr., M.D., on right in photo at left, was installed during the June Annual Meeting. During award ceremonies during the President's Banquet, he presented outgoing President Richard L. Collins, M.D., with the cowboy hat he's wearing and other gifts in appreciation of his service to the Association. Officers elected by the House of Delegates were President-Elect Joseph W. Hanss, Jr., M.D.; Vice President William J. Mangold, Jr., M.D.; and Jacqueline A. Chadwick, M.D., Treasurer. ArMA records indicate that Dr. Ivey, the Association's 100th President, is its youngest, and that Dr. Chadwick is the first woman elected to ArMA's Executive Committee.

Stanley P.L. Leong, M.D., of Tucson recently received a three-year appointment as Cancer Liaison Physician for the Cancer Program at University Medical Center, Tucson. The Cancer Liaison Program is an integral part of the Commission on Cancer of the American College of Surgeons.

Dr. Leong is among a national network of 2,300 volunteer Cancer Liaison Physicians who provide leadership and support to the Hospital Cancer Program, and other Commissions on Cancer activities.

Dr. Leong, who has a significant interest in the diagnosis and treatment of patients with malignant diseases, also provides local leadership for the annual national clinical goal of the Cancer Liaison Program; the 1989 goal is the promotion and utilization of tumor nodes metastases staging.

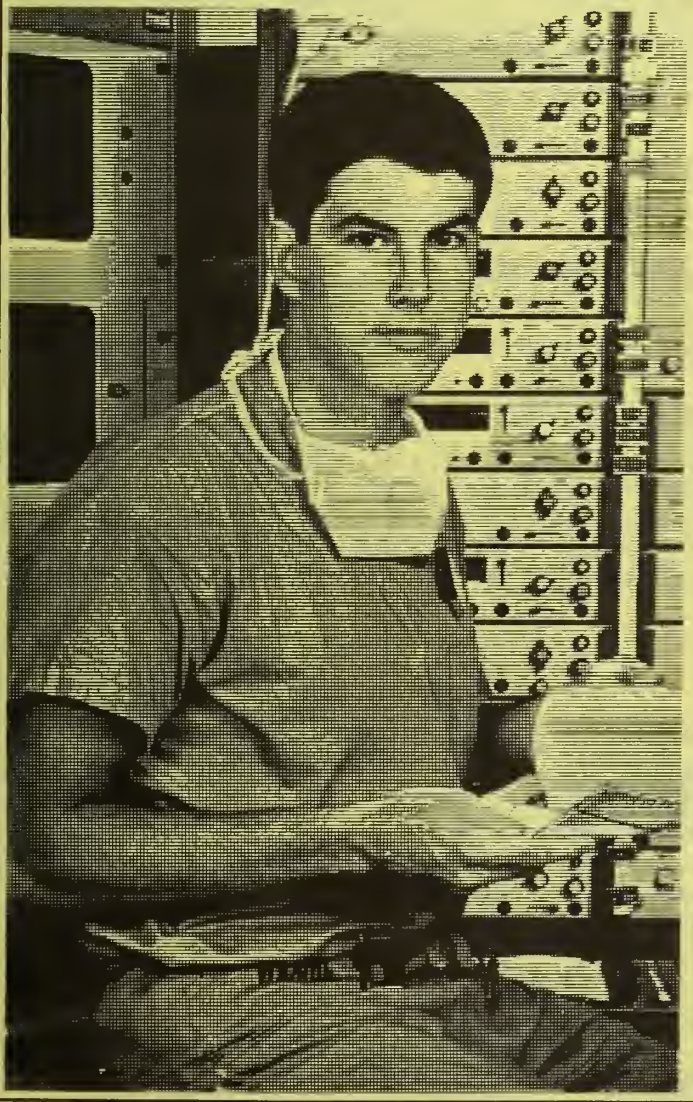
Established in 1956, the Commission on Cancer, which is composed of Fellows of the College and liaison members representing 23 other cancer-related organizations, has approved more than 1,200 cancer programs in hospitals across the country. The Commission reviews each hospital's cancer program for conformity to high standards set by the Commission, and encourages participating hospitals to equip and staff themselves so that they are able to provide the best in the diagnosis and treatment of cancer.

Recognizing that cancer is a complex group of diseases, the Cancer Liaison Physician promotes extensive communications and consultation among family physicians, surgeons, medical oncologists, diagnostic and therapeutic radiologists, pathologists, and other cancer specialists as a means of providing better patient care.

An integral part of a hospital's cancer program is its tumor registry. The Cancer Liaison Physician provides support and technical expertise to the hospital's tumor registrar and encourages medical staff at his or her institution to use data generated by the registry. All patients who are diagnosed as having cancer or are being treated for the disease are listed in the registry so that the hospital can maintain contact with them and make sure that they receive continuing care and assistance with rehabilitation.

Information collected through the registry allows Dr. Leong's institution to participate in national studies that are designed to improve patient care. Each year since 1976, more than 500 hospital cancer programs have collaborated with the Commission on these studies. Some of the most extensive incidence and survival statistics in the world have been amassed through this nationwide effort, resulting in the publication of 54 manuscripts in professional journals.

PHYSICIANS, THERE ARE TWO KINDS OF FLEXIBILITY IN THE ARMY RESERVE WE THINK YOU'LL LIKE.



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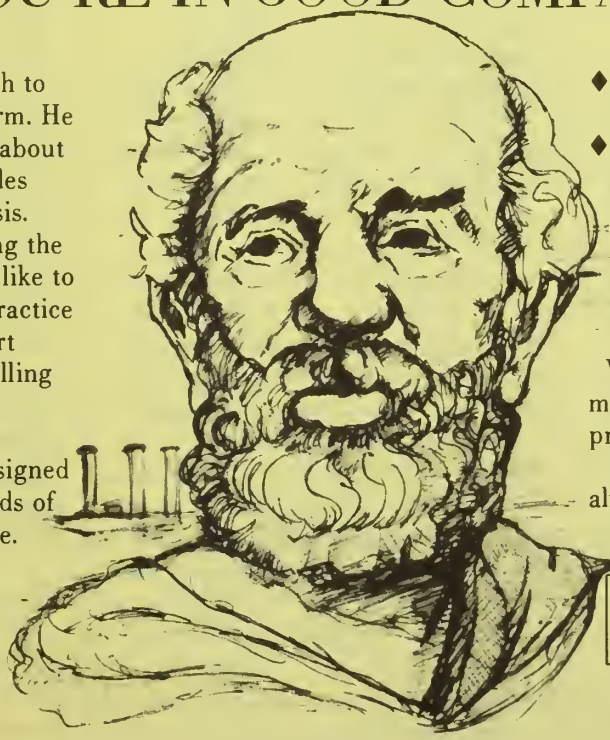

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Computer Assisted Laser Imaged Custom Hip Replacement

Since the first successful hip replacement surgery was performed in 1962, more than two million individuals have benefitted from this procedure. This year alone, 140,000 Americans will require a total hip arthroplasty.

In the past, surgeons have had to shape the femoral cavity to fit a pre-manufactured prosthesis, sacrificing valuable bone stock in the process.

Now there is a system that utilizes computer-aided technology and design (CAD/CAM) to actually create a custom implant while the patient is on the operating table. Called the Laser Imaged Computer Assisted (LICA) custom hip, the system generates a prosthesis in about 45 minutes.

To create a LICA hip, the surgeon first prepares the joint in the usual way by removing the diseased socket, ball and a small portion of the femur to expose the cavity. Liquid elastomer is then injected into the cavity inside a flexible metal form and rubber sleeve to form a mold of the femoral component. The mold indicates not only the individual contours of the patient's femoral cavity, but also the neck length and desired orientation of the neck of the femoral component.

The hardened mold is removed approximately seven minutes later and is taken to a self-contained manufacturing facility near the operating room.

The dimensions of the mold are laser-scanned into a computer, which calculates the optimum size and shape of the implant.

A two-dimensional diagram of the proposed prosthesis is printed out and delivered to the surgeon in the operating room, so that any changes or adjustments can be made prior to manufacturing.

After approval by the surgeon, the computer guides high-speed, precision milling of a titanium preform to the exact specifications. Meanwhile, the surgeon prepares the acetabulum and inserts the cup in preparation for the femoral component.

The completed prosthesis is carefully examined for quality and accuracy, then delivered to the operating room where it is sterilized and surgically implanted in the normal way. Reduction is carried out to assess the best head component.

Because the LICA implant is designed to exactly correspond to the contours of each individual's femoral cavity, the joint replacement immediately achieves at least 90% contact with the bone. Histological studies after a post-mortem examination of a patient who died of unrelated causes revealed the LICA prosthesis had achieved 100% proximal contact.

This compares to cementless implants, which average approximately 20-40% contact.

Since its initial use in Belgium, the LICA hip has been used in approximately 800 operations. Patients who have received the new implant report faster post-operative healing and less pain than conventional implant recipients.

Since in-growth of the bone is not required to stabilize a LICA implant, patients typically do not experience pain due to micro-movement of the femoral component during the healing process. Because the LICA implant does not achieve fit through cement, which has broken down after 10-15 year in a small number of cases, it is believed this implant will last for a longer period of time.

The Center of Excellence for Arthritis and Orthopaedics at Humana Hospital - Phoenix became the third place in the world to offer this new technology to patients in February 1989. The LICA custom hip is also available at a Florida Hospital and in Belgium.

Joseph A. Dupont, M.D.
Surgical Director
Center of Excellence for Arthritis and Orthopaedics
Humana Hospital - Phoenix

The Problem

Continued from page 4

Legal & Tax Aspects

OWNERSHIP may be crucial to TAXATION ...

The plan may be owned by one or both insureds, or a third party. Although there are two insureds, federal estate tax consequences are based on which individual or entity owns the policy.

Spouse Ownership

This situation depends on who dies first. If the owner-spouse dies first, the value of the policy at the moment before death would be included in the deceased's estate for federal estate tax purposes. If the non-owner-spouse dies first, there would be no estate tax implications on the first death and the full proceeds would be included in the estate of the owner who would then, of course, be the second to die.

Joint Ownership

If both insureds own the contract jointly with the right of survivorship and one spouse dies, ownership would pass to the surviving spouse. The policy values should qualify for the unlimited marital deduction and, therefore, be free of estate taxation for the first to die.

Trust Ownership

If a third party, such as a trust or adult child, were to be the owner, that arrangement would probably result in no part of the policy values being included in the estate of either spouse at their death (assuming there had been no "transfer within the three years at death").

Business Ownership

If a corporation owned a policy to provide a funding mechanism for a buy-out agreement, the proceeds would be payable to the same party, and would be received income tax free.

If the transaction were properly structured, receipt of proceeds should not cause estate tax problems by increasing the value on the deceased's stock.

Once the need for this type of coverage has been established, the cost of preserving your estate can be much less than paying all taxes and other expenses due in one lump sum at some future date.

For example: **A husband and wife, both non-smokers and age 55, have an expected federal estate tax of $1,000,000.** A Survivor Life policy with a face amount of $1,000,000 will provide the funds needed to pay the estate tax at considerably less cost. Based on a particular company's 1989 dividend scale, they could purchase a $1,000,000 policy with a little more than 8 annual payments of $15,975. Their projected policy values will be:

Total of 9 annual payments (8 of $15,975, and 1 of $1,107)	$128,907
Total 10th year death benefit	$1,168,872
Cost per dollar of death benefit	11 cents
Total 20th year death benefit	$1,271,296
Cost per dollar of death benefit	10.1 cents

For this couple, a Survivor Life policy can provide the funds to pay their estate tax with a cost of as little as 10 cents per dollar of tax due. And with the company's Enhanced Life rider, their annual premiums can be reduced to as little as $7,601 for the same $1,000,000 of coverage. And based on their 1989 dividend scale, their premiums would vanish in just over 9 years.

There is always a cost involved; there is a cost to do something now, and there is a cost to do something later.

We think it makes sense to consider this approach when planning or reviewing our estate plan.

Please call if you would like to hear more about this. It's part of the overall planning that ArMA Membership Benefits, Inc. provides.

Dick Pearson
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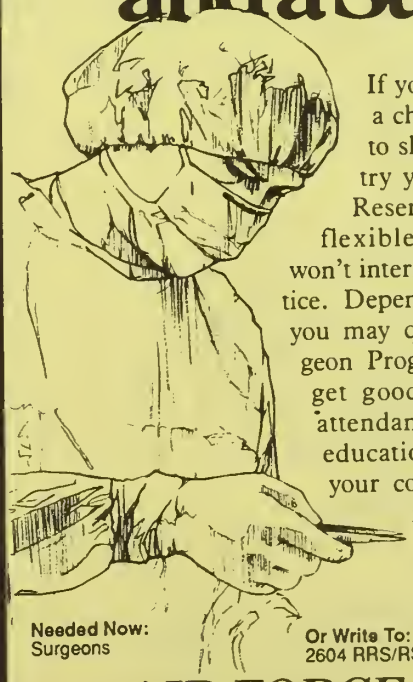

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A GREAT WAY TO SERVE

Malpractice

Continued from page 1

medical records to be reviewed by non-physicians at any time. What effect will this have an medical record keeping, medical record taking and the physician-patient relationship? For instance, will patients be willing to share their whole history with us? Will we be working with a "full-deck" when trying to unravel their problems?

In light of all of these societal influences, it is unclear to me whether we should be held liable for outcomes that are not up to society's expectations. There are those who say that our exposure should stop at negligent acts. But, when does negligence end and bad outcome begin? If society is fostering incentives for more efficient and economical care, are the bad outcomes so generated just our fault or that of society's? It would appear to me that society needs to share some of the risks with us and begin to have more realistic expectations of what we can deliver. When that takes place, perhaps a new system can be developed which will be fairer to both the givers and the receivers. We are in an upheaval affecting many facets of the delivery of health care. Society must recognize that simple push-pull responses will no longer satisfy the problem although politically it is the most expedient. Politicians are first and foremost legislators and they must be representatives of society. Local and national legislatures need to scrutinize the entire puzzle and not focus on only one or two of the parts. Unfortunately, I suspect that the solution to the problem will be politically unpalatable and will be buried because our legislatures are unwilling to come to grips with what needs to be done.

Marshall B. Block, M.D., Editor

From Our President

Continued from page 2

My hospital board and CEO question why I send some of my patients to Phoenix, *not* why this individual patient needs help that couldn't or shouldn't be provided in our rural hospital.

Well, I'm not going to cooperate with any entity or anyone who doesn't put the patient first, and you shouldn't either. Don't let health care be held hostage by administrators and the bottom line.

Patients don't want their health care determined by politicians, bureaucrats, insurance clerks or anyone other than their physicians. They're tired of waiting for days or even weeks for decisions on their health care. Let's put an immediate end to this rampant de-professionalization of medicine that is hurting the health care of America.

In Dallas at the interim meeting of the American Medical Associaiton, I heard the AMA president say "We must elect individuals who are willing to fight with those intent on destroying or controlling our profession." You did, and I want to tell you that the American Medical Association and the Arizona Medical Association are literally the only entities standing between you and socialized bureaucratically mandated medicine.

Tell your friends and colleagues to join with us. Stand up for what is right! Dedicated, strong, outspoken, caring physicians can make a difference.

We know that preservation of our profession is directly dependent upon putting the patient first. Our friends and patients trust us, their doctors, to be there, to be their number one defenders.

We must bring our patients back into the decision-making process. We are their friends and advocates. We don't lie and we don't cooperate with anyone who won't put the patient first.

From the young doctors going into practice to older physicians ready to retire, we must be united in our dedication to our patients and our profession. Together we can and will stop intrusions into the basic rights of our patients. Let us care for our patients and they in turn will care about us.

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Mark Ivey, Jr., M.D.

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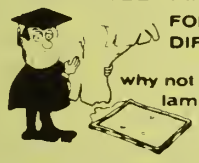

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Clinical Investigation

Multicenter Trial of Cadexomer Iodine to Treat Venous Stasis Ulcer

G. ALLEN HOLLOWAY, Jr, MD, *Phoenix;* KAJ H. JOHANSEN, MD, PhD, *Seattle;*
ROBERT W. BARNES, MD, *Little Rock, Arkansas; and* GEORGE E. PIERCE, MD, *Kansas City, Kansas*

In a crossover study designed to judge the efficacy of the topical polymeric starch iodophore, cadexomer iodine, in accelerating the healing of venous stasis ulcers, 75 patients were prospectively randomly assigned to receive either cadexomer iodine or standard treatment. The control treatment consisted of a standard saline wet-to-dry compressive dressing. The patients improved with either treatment: ulcers healed more than twice as rapidly using cadexomer iodine (n = 38) as with standard therapy (n = 37) (P = .0025). Ulcers treated with cadexomer iodine showed trends toward less pain, exudate, pus, and debris, and a more rapid development of granulation tissue. Twelve patients crossed over from control treatment to the use of cadexomer iodine because of a failure to heal, but no patients switched to control therapy from the use of cadexomer iodine (P = .01). Except for occasional mild local burning in wounds treated with cadexomer iodine, no adverse effects were noted with either regimen.

(Holloway GA Jr, Johansen KH, Barnes RW, et al: Multicenter trial of cadexomer iodine to treat venous stasis ulcer. West J Med 1989 Jul; 151:35-38)

Venous disorders are the most common ailments involving the vascular system. It is estimated that 250,000 new cases of deep venous thrombosis occur each year in the United States.[1] Many such patients go on to have the postthrombotic syndrome; more than 1% of all adults in Scotland[2] and in Switzerland[3] have been affected by venous ulceration, and perhaps as many as 500,000 stasis ulcers are treated annually in this country.[1]

Venous stasis ulcers are difficult and time-consuming to heal and commonly recur many times. While these lesions are rarely lethal, they exact an extraordinary toll in patient inconvenience, frustration, disfigurement, pain, and incapacitation. The economic cost of venous stasis ulcers in terms of time lost from work and the use of medical resources is staggering.[1-3]

Neither an optimal prophylaxis against deep venous thrombosis nor a curative treatment of chronic venous insufficiency has been identified. Thus, the current management is restricted to palliating the long-term complications of the postthrombotic syndrome. Prolonged bed rest with leg elevation will heal nearly all venous stasis ulcers, but this is costly and must be reserved for selected refractory cases, as is also true for surgical ulcer excision and grafting. Multiple topical treatments—compresses of salicylic acid; enzymes to accelerate ulcer debridement; the application of synthetic or preserved xenogeneic wound dressings; the use of steroids, antibiotics, antiseptics, or silver salts—have been found, at best, only minimally effective in controlled trials: none have been demonstrably better than the classic wet-to-dry saline compress approach.

Recently hydrophilic dextran polymer beads (dextranomer [Debrisan]) have been used topically on venous stasis ulcers, on the principle that the hygroscopic removal of wound secretions might retard surface infection and thereby accelerate wound healing and epithelialization.[4] By this process the wound surface is kept clean, but a culture medium theoretically remains in the bead interstices. Cadexomer iodine (Iodosorb [Perstorp Carbotec, Perstorp, Sweden]), a starch polymer bead similar to dextranomer but with iodide (0.9% weight per weight) bonded to the polymer, extends this principle. When fluid contacts the beads, substantial amounts of fluid—as much as 6 ml per gram of cadexomer iodine—are absorbed, as well as bacteria within the fluid. In addition, bonded iodide becomes bactericidal in this milieu. Treatment with cadexomer iodine should theoretically result in a wound that contains both less secretions and fewer bacteria, thereby promoting wound healing. We evaluated the use of cadexomer iodine in the management of venous stasis ulcers by means of a prospective, randomized crossover trial in which the use of this agent was compared with that of a standard treatment approach at three university hospitals.

Patients and Methods

In all, 75 outpatients, 55 men and 20 women, were entered into the trial at three sites—Richmond, Virginia; Kansas City, Kansas; and Seattle, Washington. Their ages

From the Departments of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle (Drs Holloway and Johansen), Virginia Commonwealth University School of Medicine, Richmond (Dr Barnes), and University of Kansas Medical Center School of Medicine, Kansas City (Dr Pierce).

Dr Holloway is currently with the Maricopa Medical Center, Phoenix, and Dr Barnes is with the University of Arkansas College of Medicine, Little Rock.

Technical assistance was provided by Molly Zaccardi, Glenn Turley, Linda Klein, RN, ET, and Paul Cunningham.

This study was funded by a grant from T.I.L. (Medical) Ltd, Toronto, Canada.

Reprint requests to Kaj H. Johansen, MD, PhD, Department of Surgery, Harborview Medical Center, 325 9th Ave, Seattle, WA 98104.

ranged from 31 to 93 years. Informed consent, approved by each site's institutional review board, was obtained from each patient. Inclusion criteria required a patient to be in good health and to have had a venous stasis ulcer present for a minimum of three months. Initially patients with ulcers less than 2 cm in maximum diameter were excluded, but this criterion was relaxed partway through the trial. Potential subjects were excluded if there was a suspected or proven nonvenous cause of the ulcer, an inability to comply with the treatment regimen, major medical disorders, an iodine allergy, or clinically significant arterial disease.

The initial patient evaluation included a relevant history, a physical examination, and laboratory studies, with an emphasis on blood, kidney, liver, and thyroid profiles. The ulcer size was measured planimetrically on transparent tracings. Ulcers were graded as "very superficial" (through skin), "superficial" (through subcutaneous tissue), or "deep" (into or through muscle, near bone). Surface characteristics of the ulcer—quantity of exudate, pus, debris, amount and quality of granulation tissue, degree of edema, and erythema—and pain were all recorded on an analog scale, and a color photograph of the ulcer, taken at a standard distance and under controlled lighting, was obtained. Swabs of the ulcer bed for aerobic and anaerobic culture, using Stuart's transport medium modified to neutralize the iodine during subsequent treatment, were taken for bacteriologic purposes. Noninvasive arterial and venous studies, carried out to confirm the underlying venous pathophysiology, included arterial and venous Doppler, venous outflow strain-gauge plethysmography, and photoplethysmography.

After the initial studies were done, patients were randomly assigned to either the standard or cadexomer iodine treatment groups. Standard treatment consisted of wet-to-dry dressings with saline-soaked sterile 4-in by 4-in gauze pads changed by the patient once a day. In the cadexomer iodine-treated patients, the ulcer was irrigated with a saline solution, the medication was sprinkled onto the ulcer, and the wound was covered with a dry gauze dressing. This treatment was repeated on a daily basis by the patient. In both groups the dressing was held in place by a toe-to-knee elastic compression bandage.

Follow-up was at two-week intervals for the first eight weeks and then at monthly intervals. Each ulcer was evaluated serially by the same person at each medical center. Patients were removed from the study when their ulcer healed or if it was felt by the attending physician that, due to worsening of the ulcer, more intensive therapy—that is, operative excision and grafting—was needed. At each visit a bacteriologic swab was taken, the ulcer was measured and traced, and a photograph taken. Ulcer healing was expressed in square centimeters per week and in square centimeters per week per centimeter of baseline ulcer circumference. At 12 weeks, the physical examination and the general laboratory studies were repeated. Also, if the ulcer was not healed at this time, the patient was offered the opportunity to switch to the alternate therapy group. Patients were questioned about compliance at each visit.

When an ulcer was healed, or at the end of 24 weeks, the patient was reexamined, laboratory tests were done, and the ulcer was reevaluated in the vascular laboratory in the same manner as at the beginning of the study.

Data from all patients were serially collated for statistical analysis. The Student's *t* test was used for comparing pretrial baseline studies and laboratory studies. An analysis of covariance was used for assessing differences in the healing rate. Statistical significance was assumed for *P* values of less than .05.

Results

Of the 75 patients starting the trial, 15 did not complete the study for reasons other than healing of the ulcer. Four failed to respond to one or both treatments and required more aggressive treatment. Two died during the study of causes unrelated to their ulcers, and nine dropped out or failed to return. An additional six patients were excluded from the statistical analysis. Two of these were felt in retrospect to have been inappropriately entered into the study because their ulcers were too small. The other four lacked adequate follow-up information. Subjects failed to complete the study or were excluded from analysis in equivalent proportions from the control and cadexomer iodine-treated groups, and noninclusion did not appear to influence the study's analysis or conclusions. A total of 54 patients remained from whom data were available for statistical analysis.

The two treatment groups were similar in all baseline characteristics, although the mean ulcer duration before treatment was considerably greater in the cadexomer iodine-treated group than in the control group (Table 1). The mean ulcer area was substantially—although not significantly: $P = .11$—greater in the cadexomer iodine-treated group, primarily due to randomization to this group of two patients with giant ulcers measuring 136.2 cm^2 and 127.3 cm^2, respectively.

Ulcer healing was significantly ($P < .0001$) different from zero in both the control and the cadexomer iodine treatment groups at all three centers. The healing rate for patients undergoing standard treatment was 0.41 cm^2 per week, compared with 0.95 cm^2 per week in those treated with cadexomer iodine ($P = .0025$; Table 2). This healing advantage achieved statistical significance both in the overall group and at two of the three individual centers; the *P* value at the third center was .09. Healing as a proportion of the baseline ulcer circumference approached statistical significance in the cadexomer iodine-treated group ($P = .072$). Overall, treatment with cadexomer iodine accelerated healing 1.5 to 2.5 times compared with standard treatment. A trend toward improvement in terms of enhanced granulation and diminished

TABLE 1.—*Patient Characteristics*

Patient and Ulcer Characteristics	*Ulcer Treatment*	
	Standard (n=37)	*Cadexomer Iodine (n=38)*
Male, No.	27	28
Female, No.	10	10
Age* (range), yr	61.5±12.7 (31-84)	63.0±0.8 (34-93)
Duration of ulcer, mo*	11.4±21.8	29.5±59.1
Median (range)	4.5 (3-130)	7.5 (3-240)
Area of ulcer, cm^2		
Mean	11.20	20.05
Median (range)	9.75 (3.0-37.0)	10.70 (0.6-136.0)
Depth of ulcer†		
Deep	13	18
Superficial	17	15
Very superficial	7	5

*Plus or minus standard error of the mean.
†See text (Methods section) for description of depth.

edema, pain, exudate, pus, and debris was also noted with the use of cadexomer iodine; this trend did not achieve statistical significance (Table 3).

As expected, numerous bacterial species were isolated from the ulcers. Neither treatment was superior in causing a reduction in bacterial numbers on a semiquantitative (categorized as profuse, moderate, or sparse) basis. A persistence of pathogenic organisms, even at levels often associated with invasive infection,[5] was frequently associated with rapid healing. On the other hand, the presence of β-hemolytic streptococci was almost invariably associated with a failure to heal[6]; only one patient with cultures positive for streptococci had ulcer healing.

A total of 12 patients switched treatments during the trial: all 12 crossed over from the control treatment to using cadexomer iodine because of a failure of healing, but no patient switched to control therapy from cadexomer iodine (P = .01, Fisher's exact test). Of the 12 patients, 5 did not benefit from the crossover, and the other 7 showed healing of their ulcers.

Only minimal adverse effects were noted with cadexomer iodine treatment and none with the control treatment. Six patients had mild transient burning, pain, or itching associated with using cadexomer iodine. No other symptoms could be related to the experimental treatment.

Although there were insignificant changes in serum chemistry values in both study groups, no specific patterns or correlations with treatment were seen. Of specific interest, no significant changes in thyroid function were seen in either group.

Discussion

Browse and Burnand have proposed that venous stasis ulcers occur when the pathologically altered venous hemodynamics of the postthrombotic syndrome result in the interstitial deposition of fibrinogen, with subsequent fibrosis, cutaneous ischemia, skin breakdown, and ulcer formation.[7] Ideally, venous function might be improved to allow healing of venous stasis ulcers, but this is usually not possible or, at least, not feasible, and clinicians are left to deal with the chronic ulcerative complications of the postthrombotic syndrome.

We evaluated the ability of a starch polymer iodophore, cadexomer iodine, to accelerate the healing of venous stasis ulcers. The results of a three-center randomized crossover trial indicate that both standard saline wet-to-dry and cadexomer iodine treatments are effective in reducing ulcer size and promoting healing. Treatment with cadexomer iodine healed ulcers significantly more rapidly than standard treatment, a finding in accordance with two previous European trials.[8,9] In our study, the mean ulcer healing rate was more than twice as great with the use of cadexomer iodine as with the control treatment.

The cleansing action of the two treatments was evaluated on visual analog scales that assessed the amount of exudate, pus, and debris at the ulcer surface. Both treatments appeared to be highly effective in improving wound appearance: cadexomer iodine appeared to be more effective, although not at the level of statistical significance. Removing exudate and dead tissue, both of which provide an excellent bacterial culture medium, presumably results in a better environment for epithelialization and healing. Pain and edema were also substantially reduced by both treatments, again with a trend favoring the use of topical cadexomer iodine.

Bacteriologic studies showed that in both treatment groups the number of organisms decreased during the study, with neither showing superiority. It is unclear, however, whether this represents a response to the topical treatment or, alternatively, a response to an improved healing process. A decrease in the number of organisms was commonly associated with healing. On the other hand, ulcers often healed despite the persistent presence or even profuse growth of pathogenic organisms. This apparently occurs because most such bacteria primarily colonize the superficial exudate and debris of the venous stasis ulcer. The presence of β-hemolytic streptococci, however, was associated with a failure to heal in all but one patient. This is in keeping with previous experience[6] and presumably occurs because this organism is tissue-invasive. These results support the systemic use of antibiotics in patients having β-hemolytic streptococci on venous stasis ulcer culture.

No significant adverse effects were noted during the trial other than mild transient local burning noted by a few of the cadexomer iodine-treated patients. This has been reported in other trials using iodine-containing compounds but has not been associated with other or more severe effects. None of the laboratory safety monitoring—hematology, clinical chemistry, urinalysis, or thyroid function—showed any consistent changes that could be related to the treatment.

This trial shows that both standard wet-to-dry dressings and the topical use of cadexomer iodine promote the healing of venous stasis ulcers. In this study, the latter was more than twice as effective (P = .0025) in promoting healing. Both treatment methods appear to improve the environment for healing by cleaning the ulcer surface and thereby accelerating the development of ulcer granulation tissue and epithelialization. Comparing the use of cadexomer iodine with other recently introduced topical agents or treatments might further delineate the means by which venous stasis ulcers heal. Topical cadexomer iodine may be a useful addition to

TABLE 2.—*Response to Treatment and Ulcer Healing*

Treatment Response	Treatment* Standard	Treatment* Cadexomer Iodine	Difference Between Treatments, P Value
Ulcer healing, cm^2/wk	0.41±0.13	0.95±0.12	.0025
Ulcer healing vs baseline circumference, $cm^2/wk/cm^2$	0.03±0.01	0.04±0.01	.0720

*The numbers show the mean rate of change plus or minus the standard error of the mean.

TABLE 3.—*Response to Treatment*

Ulcer Characteristics	Treatment* Standard	Treatment* Cadexomer Iodine	Difference Between Treatments, P Value
Granulation	2.75±0.4	3.43±0.3	.16
Edema	−1.40±0.2	−1.60±0.2	.53
Pain	−2.44±0.4	−2.47±0.3	.96
Exudate	−2.51±0.3	−3.11±0.3	.20
Pus and debris	−2.43±0.3	−2.68±0.3	.55
Erythema	−1.86±0.3	−1.14±0.3	.06

*The numbers show the mean rate of change plus or minus the standard error of the mean.

the therapeutic armamentarium of clinicians treating patients with venous stasis ulcers.

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Pupil Response

In nontraumatic coma, excluding drug-induced coma, one can perhaps make some prognostication on the best recovery at one year by noting the presence or absence of the pupil response, corneal reflex, or caloric response at the time the patient is admitted. If two or more of these are absent, only 1% of these patients at one year will have moderate disability to good recovery. Of these patients 99% will either have no recovery—they've died—vegetative state, or perhaps severe disability.

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—LENWORTH N. JOHNSON, MD

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Clinical Medicine

Diagnosing Dislocation of the Hip in Infancy

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In evaluating the diagnosis of dislocation of the hip in childhood by orthopedists in Oregon in 1985, we identified 36 dislocations in 32 patients, an incidence of 0.9 per 1,000 live births. In 12 patients, 12 dislocations (33%) were diagnosed after the neonatal period, 5 of which were diagnosed at walking age. Of the 12 children with a late diagnosis, 10 had normal hips when examined in the neonatal period. Neonatal screening will not detect all cases of congenitally dislocated hip. If dislocation of the hip in childhood is to be diagnosed in a timely manner, it is essential that children's hips be examined at the time of routine well-baby evaluations until a normal gait has been established.

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The single most important factor controlling the prognosis of dislocation of the hip in children is the age at diagnosis.[1,2] Screening protocols have emphasized the techniques of examining a newborn. These techniques have decreased but not eliminated the incidence of the late diagnosis of hip dislocation. We now recognize that the diagnosis in a newborn may be missed by the most experienced examiners and that dislocation may occur after the neonatal period.[3-5] This requires modifying the accepted examination strategy if we are to diagnose hip dislocation in a timely manner. Few studies have been done to determine the efficacy of neonatal examination in the diagnosis of congenital dislocation of the hip (CDH) in the United States.[6-8]

In this study we review all cases of congenital hip dislocation in children born in Oregon in 1985 who were seen by orthopedists. The purposes of this study were to determine the incidence of CDH treated by orthopedists in Oregon, to determine the proportion of "late" diagnosis of the disorder, to provide recommendations for terminology and examination techniques, and to suggest an examination strategy to diagnose dislocation of the hip at an early age.

Patients and Methods

The data in this study were collected retrospectively over a two-year period, 1986 through 1987. Each of the 240 practicing orthopedic surgeons in Oregon was contacted by mail requesting permission to review cases of congenital hip dislocation they had seen during 1985. Of the 240 orthopedic surgeons, 220 responded (92%), 54 indicating that they had evaluated patients for congenital hip instability during that time period. The medical records and radiographs were reviewed by one of us (J.R.H.). Only patients born in the state of Oregon in 1985 were included in this study. Data collected included the age at diagnosis, the sex, the involved side, and the method by which the diagnosis was established. In the cases of a late diagnosis, the circumstances leading to an orthopedic evaluation were recorded.

Dislocation of the hip was diagnosed if the examining orthopedist observed that the hip was dislocated, a positive Ortolani's sign was described, or if there was radiographic evidence of dislocation.

Results

A total of 36 hip dislocations were identified in 32 children born in 1985. Four patients had bilateral dislocations. There were 39,429 live births in Oregon in 1985, implying an incidence of dislocation of 0.9 per 1,000 live births. Dislocation occurred in 26 girls and 6 boys; 27 dislocations occurred in the left hip and 9 in the right hip.

Neonatal Diagnosis

Dislocation of the hip was diagnosed in the neonatal period in 20 patients, 4 bilateral, for a total of 24 instances—67% of all dislocations. All 20 patients were referred by the primary care physicians for orthopedic evaluations. The diagnosis was established by physical examination in 16 patients. Dislocation was suspected clinically in eight others and confirmed by radiographs. All 20 patients were treated by placing in a Pavlik harness.

Postneonatal Diagnosis

A total of 12 dislocations were diagnosed in 12 patients after 4 weeks of age—33% of all dislocations (Table 1). In seven of these cases of late diagnosis, dislocation was ascertained between 1 and 6 months of age. In four (cases 1 through 4) a pathologic disorder of the hip was noted by the primary care physician during a well-baby examination. Two cases (cases 5 and 6) were diagnosed by orthopedists when referred for evaluation of foot deformities, and one patient (case 7) was brought to the pediatrician by the parents because of an audible hip click noted during diaper changes. Six of these patients were satisfactorily treated with closed reduction, and the seventh required open reduction.

The other five cases were discovered at walking age. Four of the five children presented to their primary care physician because of a limp or leg-length discrepancy noted by the parents (cases 9 through 12). One of the patients (case 11) was known to have had a dislocated hip at birth. Treatment in

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TABLE 1.—*Late Diagnoses of Hip Dislocation*

Case	Age at Diagnosis, mo	Indication for Referral	Who Noted Problem	Results of Neonatal Examination	Treatment
1	2	Unstable hip	Pediatrician	Normal	Pavlik harness
2	3	Valgus feet	Pediatrician	Normal	Pavlik harness
3	3	Unstable hip	Pediatrician	Normal	Pavlik harness failed; closed reduction, 9 mo
4	3	Unstable hip	Pediatrician	Normal	Closed reduction
5	4	Out-turned feet	Pediatrician	Normal	Frejka pillow splint
6	4	Limited abduction	Pediatrician	Normal	Failure of closed abducted reduction; open reduction; femoral osteotomy
7	4	Mother noted hip click	Parents	Normal	Closed reduction
8	10	Unstable hip	Parents	Dislocation	No initial treatment; closed reduction at 10 mo
9	12	Leg-length discrepancy	Parents	Normal	Closed reduction
10	12	Limp	Parents	Normal	Closed reduction; femoral osteotomy
11	14	Limp	Parents	Dislocation	Pavlik harness for 1 mo; open reduction, 14 mo
12	15	Limp	Parents	Normal	Closed reduction; adductor tenotomy

a Pavlik harness had been initiated but was discontinued by the parent(s), and no further follow-up occurred until the child was seen again at 14 months of age with a dislocated hip. The fifth case of late diagnosis (case 8) was a child brought in by the parents at 10 months of age, with the concern that a dislocated hip noted at birth had not been fully addressed because of more urgent concerns with severe congenital heart disease. There were no bilateral dislocations in the late-diagnosis group. Four of these cases of late diagnoses were treated satisfactorily by closed reduction. One patient (case 11) required open reduction.

Discussion

This study suggests an incidence of congenital dislocation of the hip in Oregon of 0.9 per 1,000 live births. This is less than the incidence of 1.3 to 3 per 1,000 live births reported in other studies.[6,9–11] The discrepancy is likely due to several factors. This study assumes that all congenital hip dislocations are evaluated by orthopedists and relies on the retrieval system and compliance of the surveyed orthopedists. Further, because the patients were between the ages of 1 and 2 years at the time of the study, it is possible that additional cases of late CDH will be ascertained from that population. Nonetheless, this population of children with dislocation of the hip is thought to be representative of the present experience in diagnosing congenital dislocation of the hip.

Late Diagnosis of Dislocated Hip

Several reports in the literature indicate that despite careful neonatal screening, no country has eliminated the late diagnosis of CDH.[10,12–15] The incidence of the late diagnosis (after 4 weeks of age) of CDH in this study is 0.3 per 1,000 live births and represents a third of all ascertained cases of CDH. The reported worldwide incidence of a late diagnosis of CDH ranges from 0.07 to 2.0 per 1,000 live births.[8,13,14,16]

The difficulty of diagnosis in the neonatal period is shown by the high "failure" rates of both experienced pediatricians and orthopedists in detecting early CDH. Bialik and coworkers reported a series of 23,892 infants screened independently by an orthopedist and a pediatrician.[16] Hip instability was recognized by both examiners in 51 infants, but 25 additional cases of dislocation were detected by one examiner and missed by the other.

Some "missed" cases of CDH occur in premature or severely ill children whose hips are not carefully examined because of more urgent medical concerns. Hansson and associates found that 55% of missed cases of CDH in Sweden during the 1960s were in newborns who required treatment in the neonatal intensive care units.[10]

There is growing evidence that hips normal at birth dislocate after the neonatal period. Westin and colleagues have documented this phenomenon and termed it developmental hip dislocation.[17] It has been suggested that in some patients dysplastic hips and a tendency to dislocate develop after the first month of life. Wynne-Davies observed acetabular dysplasia in the parents of children in whom the diagnosis of CDH was made after the neonatal period.[18] This phenomenon did not occur in the parents of children diagnosed in the neonatal period. She postulated that hip dysplasia and dislocation may develop in infancy in genetically susceptible children. Davies and Walker observed ten children who had clinically stable hips at birth but who also had risk factors for CDH (family history, breech presentation, calcaneovalgus feet).[19] Radiographs taken at 1 month of age showed acetabular dysplasia in all ten cases. Four of these patients subsequently had dislocation. These studies clearly show that not all cases of hip dislocation in children are present at birth and that a late diagnosis is relatively common.[20]

In this study, 12 of 36 cases of dislocation were diagnosed after the neonatal period. In only 2 of the 12 cases (cases 8 and 11) was an abnormality noted in the neonatal hip examination. In the remaining ten cases the results of neonatal hip examinations were normal.

We found two clinical subsets of patients with a late diagnosis of CDH. Seven children were diagnosed between 1 and 6 months of age. Six of these seven children were referred to orthopedists by their primary care physicians for possible hip or foot deformities noted at well-baby examinations. The remaining five late cases were diagnosed at walking age when the parents noted an abnormal gait. This implies that if CDH is not diagnosed during the first six months of life, it will not be diagnosed until walking age. A recognition of CDH at walking age is associated with more complex treatment and a less favorable prognosis.[11,21–23] Two of the cases of late diagnosis (cases 8 and 11) can be attributed to insufficient follow-up of patients with known hip instability. The other ten cases of late diagnosis are due to either a missed congenital dislocation or developmental dislocations.

Examination of the Newborn

Three reliable physical signs assist in diagnosing hip instability in the neonate: the Ortolani test, femoral pistoning, and the Barlow test.[24] The Ortolani test is done on a relaxed

infant in the supine position.[25] The thumb is placed adjacent to the lesser trochanter, and the fingertips are placed over the greater trochanter. One hand stabilizes the pelvis, and the examining hand flexes the hip to 90 degrees and gently abducts the hip. If the hip is dislocated, the femoral head can be felt to move anteriorly into the acetabulum, a positive Ortolani's sign.

Femoral pistoning is ascertained with the supine infant's hip flexed 90 degrees. One hand stabilizes the pelvis, and the examining hand is placed around the flexed knee, exerting a gentle push-pull action. If the femoral head is dislocated, a pistoning effect is observed as the posteriorly dislocated femoral head is pulled anteriorly to the acetabulum and pushed back to the dislocated position.

The Barlow test is a provocative maneuver to determine that a hip is dislocatable or subluxable.[21] With the infant and examiner in the same position as in the Ortolani test, the hip is flexed to 90 degrees and adducted past the midline. Gentle downward pressure is exerted on the femur. When a hip is unstable, the femoral head can be felt to move posteriorly out of the acetabulum partially (subluxable) or completely (dislocatable). Unstable hips may yield subtle findings, and the importance of a gentle and careful examination cannot be overemphasized.

The presence or absence of asymmetric thigh folds is of no diagnostic value.[26] Hip clicks elicited in the neonatal period without other signs of instability are not abnormal. Most hip clicks in neonates are extracapsular, arising from adjacent soft tissues.[11,27]

Following the neonatal period, the examination of an infant with a dislocated hip yields different findings because of secondary soft tissue changes. Persistent dislocation leads to contracture of the adductor muscles. The most reliable signs at this time are limited hip abduction, pistoning, and apparent limb shortening or asymmetry of the involved side. An inability to reduce the dislocation in the presence of soft tissue contractures may lead to a negative Ortolani test. If elicited, however, the findings of the Ortolani test may change from a proprioceptive sensation of reduction to a palpable and audible "clunk" of entry as the femoral head enters the socket.

Terminology

The term dislocation should be reserved for those hips that are truly dislocated—that is, in patients who have an Ortolani's sign, who show femoral pistoning, or who have radiographic evidence of dislocation. Dislocatable refers to a hip that is reduced but that can be dislocated by the Barlow maneuver. Subluxation refers to a hip that moves abnormally in the acetabulum on clinical examination or radiographically. Dysplasia describes the radiographic changes associated with a failure of normal development of the acetabulum, femur, or both.

A radiographic evaluation in a newborn to detect CDH is of limited value, as much of the pelvis is cartilaginous and radiolucent. After 4 to 6 weeks of age, radiographic evaluation is more useful. The most reliable roentgenograph in infancy is a single anteroposterior film of the pelvis with the legs abducted 45 degrees and the thighs internally rotated (the von Rosen view).[28] A line drawn along the long axis of the femur will contact the pelvis above the rim of the acetabulum when the hip is dislocated. Imaging techniques using ultrasonography and magnetic resonance imaging are presently being investigated, but the routine use of these procedures is not yet validated.[29,30]

Recommendations

An examination of the hips should be a part of the routine well-baby examination from birth to walking age. In examining the hips in a neonate, the clinician should search for the Ortolani's sign of entry and femoral pistoning, and, if they are not present, do the Barlow test for instability. The examination after the neonatal period should involve looking for apparent limb shortening, limited abduction, and femoral pistoning. A radiographic examination after the neonatal period is a simple and accurate means to confirm the diagnosis of a dislocated hip.

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Placebo-Controlled Trial of Quinine Therapy for Nocturnal Leg Cramps

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A prospective, double-blind, placebo-controlled crossover study of the use of quinine for nocturnal leg cramps was carried out in 8 elderly volunteer patients. The patients were randomly assigned to receive either placebo or 200 mg of quinine sulfate by mouth at bedtime. After 4 weeks of treatment and after a one-week washout period, the group taking quinine switched to placebo and vice versa for another 4 weeks. The differences in the number, duration, and severity of cramps and the side effects were compared. All of the patients had fewer cramps and decreased severity and duration of attacks while receiving quinine. Mild side effects developed in only 2 patients, and these subsided without treatment or discontinuing the medication. We conclude that quinine was effective in relieving nocturnal leg cramps in a selected group of elderly patients.

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Nocturnal leg cramps are a common clinical problem seen most frequently in the elderly. Although there have been many hypotheses to explain the cause of these night cramps, the pathophysiology is still poorly understood. Currently many therapeutic approaches are offered. Some patients may benefit from measures such as raising the foot of the bed or dorsiflexing the feet.[1-3] The most commonly prescribed medication is quinine sulfate. Some clinicians think that it is effective and prescribe it on an empiric basis, even though there is no scientific consensus concerning its efficacy or mechanism of action.

Quinine therapy was reported in early studies from the 1930s and 1940s to be effective in relieving nocturnal leg cramps.[4-6] Unfortunately, these studies were based on uncontrolled data and suffered from inadequacies in their designs. More recent controlled studies have shown contradictory results. Jones and Castleden reported in 1983 that the use of quinine was superior to that of placebo in patients with night cramps,[7] but in 1987 Warburton and co-workers claimed that using quinine was no better than giving a placebo.[8] In view of this controversy, we studied quinine therapy in a prospective, double-blind, placebo-controlled crossover study in patients with nocturnal leg cramps and herein report the results.

Subjects and Methods

We screened patients with nocturnal leg cramps who came to our internal medicine clinic from June to December of 1987 and recruited 15 volunteer outpatients to participate in the study. All of the patients had at least a one-year history of night cramps that were not relieved by traditional approaches. Each patient reported an average of at least two cramps per week. Patients were included only if they did not have any identifiable cause of muscle cramps such as neuromuscular diseases, an electrolyte imbalance, atherosclerotic peripheral vascular disease, or the concomitant use of nifedipine or terbutaline sulfate—all of which have been reported to induce leg cramps. Exclusion criteria were as follows: a known or suspected hypersensitivity to quinine or glucose-6-phosphate dehydrogenase deficiency, a history of optic neuritis and tinnitus, impaired liver or kidney function, or a concurrent use of muscle relaxants, narcotics, nonsteroidal anti-inflammatory agents or other analgesics that may influence the results of the study. Before the beginning of the study, all subjects received a physical examination and selected screening laboratory studies—complete blood count, urinalysis, and serum electrolyte determinations. Each subject gave an informed written consent.

The design of the study included a four-week treatment period followed by a one-week washout time and crossover to a second four-week treatment period. The study was done on an outpatient basis, and patients were randomly assigned in a double-blind manner to begin receiving either quinine sulfate (Quine 200, Reid-Rowell Company, Marietta, Georgia) or a placebo. Each subject was asked to take either 200 mg of quinine or placebo by mouth at bedtime every night for the first four weeks and then was switched over to the other regimen for the second four weeks. Patients were interviewed every week during the study to assess the number of cramps, the severity and duration of each attack, and any side effects experienced. They were asked to keep a diary of these events. Patient compliance was also addressed during each interview and was further assessed by counting the number of pills left at the end of the study.

The results in each trial period were assessed and compared in three categories: the total number of cramps, the cumulative duration of attacks in minutes, and the cumulative scores of the severity of the attacks, with three different intensity scores—1 signifying mild, 2 moderate, and 3 se-

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TABLE 1.—*Number, Duration, and Severity of Leg Cramps With Quinine Sulfate Therapy Versus Placebo*

Patient No.	Age, yr	Sex	No. of Cramps		Cumulative Duration of Cramps, min		Cumulative Scores of Severity*	
			Quinine	Placebo	Quinine	Placebo	Quinine	Placebo
1 . .	47	♀	3	6	3	6	3	9
2 . .	56	♀	0	8	0	12	0	12
3 . .	56	♀	2	6	2	6	4	11
4 . .	67	♀	1	5	1	14	1	9
5 . .	71	♀	0	12	0	70	0	25
6 . .	68	♂	2	14	12	64	4	25
7 . .	81	♀	2	13	11	255	6	45
8 . .	61	♀	3	8	13	47	5	17
Wilcoxon's signed rank test			$P<.01$		$P<.01$		$P<.01$	

*The severity of attacks was scored as follows: 1=mild, 2=moderate, 3=severe.

vere. The results of each period were then compared and analyzed by Wilcoxon's signed rank test.

Results

Of the original 15 patients recruited for the study, 6 withdrew before the beginning of the trial. Another patient had a history of esophagitis and dropped out after two days—while receiving quinine—because of nausea. One man and seven women with a mean age of 63 years—range, 47 to 81 years—completed the study. Compliance was good in all patients.

Number of Cramps

Table 1 shows the results of the trial of quinine therapy and the placebo trial. There was a significant reduction in the number of cramps in all patients when they were taking quinine ($P<.01$). In two patients there were absolutely no cramps in the entire four-week period while they were on quinine therapy.

Although all patients claimed to have an average of at least two cramps per week before the trial, three patients had fewer than eight cramps during the four weeks when they were receiving a placebo. Even if the results in these three patients were excluded, however, the difference between the quinine and placebo trial is still statistically significant ($P<.01$).

Duration of Cramps

The duration of each attack (in minutes) was added together in each period and is compared in Table 1. Again, there was a significant reduction in the total duration of cramps in all patients when they were taking quinine ($P<.01$).

Severity of Cramps

Each attack of cramps was assessed by a scale using three intensity scores. The cumulative total of the scores in each period was compared, and the scores are shown in Table 1. Again, there was a significant reduction in the severity of cramps in all patients when they were receiving quinine ($P<.01$).

Side Effects

Only two patients experienced some mild side effects. Patient 3 had tinnitus for two days in the second week when she was on quinine therapy. Patient 5 had blurred vision for one day in the third week when she was receiving quinine. In both patients, the symptoms subsided spontaneously without stopping the medication. In general, quinine was well tolerated by our patients.

Discussion

Nocturnal leg cramps are common in the elderly population. One manufacturer of quinine has claimed that "one out of seven people over the age of 45 years occasionally suffers from night cramps."[9] Many hypotheses are offered to explain the pathophysiology of nocturnal leg cramps: venostasis due to varicose veins,[1] accumulation of metabolites in the lower extremities,[2] and muscle hypoxia.[7] There are no data to support these hypotheses, however. Some medications have been reported to provoke night cramps. For example, Zelman reported in 1978 that terbutaline could induce night cramps that could be reversed by drug withdrawal.[10] In 1982 Keidar and colleagues reported a similar finding with nifedipine therapy.[11]

Quinine has long been used as an effective antimalarial agent. It also has analgesic and muscle relaxant properties. Over the past few decades, it has become increasingly more common for clinicians to use this agent in the treatment of nocturnal leg muscle cramps.[12] Although many clinicians think that quinine is effective in relieving leg cramps, there are no conclusive data to support its use. Early studies in the 1930s and 1940s such as those of Gootnick, Harvey, and Moss and Hermann claimed that quinine therapy was effective.[4-6] Unfortunately, early studies were based on uncontrolled data and suffered from inadequacies of design.

In 1976 Kaji and associates studied the effect of quinine use in nine patients with leg cramps who were on maintenance hemodialysis therapy. They found that the use of quinine was more effective than placebo in this specific patient population in reducing the frequency of cramps, but quinine apparently did not alter the severity of the cramps. Recently reported studies, however, have been contradictory. Jones and Castleden in a double-blind crossover study in nine patients found that quinine was superior to placebo in relieving night cramps.[7] Warburton and co-workers found that there was no statistically significant difference between quinine and placebo use in the 22 patients they studied.[8] In 1986 Lim, reporting on 25 inpatients, noted that quinine therapy was ineffective in reducing leg cramps.[14]

In view of these contradictory data, we attempted to investigate the effectiveness of quinine therapy. Quinine sulfate is available in many doses. To minimize side effects and possible drug interactions, we chose to give 200 mg of quinine instead of the higher doses that are commonly used. Serum quinine concentrations were not measured in our patients because a therapeutic serum level is not known, and a reliable method was not available locally.

We analyzed our results by determining the number, duration, and severity of cramps. Our results showed that there was a statistically significant reduction in all three of these categories when patients were taking quinine as compared with placebo. Side effects of the quinine use were also minimal. Of all the patients who participated in the study, only two experienced some side effects that subsided without the need of treatment or discontinuing the study.

Our results are consistent with the reports of Jones and Castleden.[7] Warburton and associates found quinine therapy to be ineffective in relieving leg cramps. The differences in

our results compared with those of Warburton and colleagues may be related to differences in patient populations; the definition of leg cramps and the basis of excluding patients from the studies were not comparable. Another possibility may be a longer period of treatment in our study (four weeks of taking quinine) versus a shorter period (three weeks) in their study. Third, most of our patients appeared to have a milder problem (the range of cramps was 2 to 4 cramps per week) than the patients in their study (as many as 15 cramps per week). Finally, despite the fact that overall improvement was not statistically significant in their study, Warburton and co-workers reported that "in the group as a whole, fewer cramps were reported in the early morning on quinine than on placebo."[8] The negative results in the study of Lim[14] are difficult to interpret because of problems in the study design and the reporting of the data.

The exact mechanism of action of quinine is poorly understood. It may act by decreasing the excitability of the motor end-plate region so that the responses to repetitive nerve stimulation and to acetylcholine are reduced. Quinine also increases the refractory period of muscle contraction so that the response to tetanic stimulation is diminished.[15,16]

The use of quinine has some risks.[12,15,16] Commonly reported side effects include nausea, vomiting, and diarrhea. Cinchonism has also been reported to occur from single overdoses or the repeated use of as little as 300 mg of quinine sulfate per day.

In summary, we conclude that quinine use is effective in a selected group of older patients in relieving nocturnal leg cramps. Although the number of subjects in this study was small, the results were statistically significant. Because most of the patients were women, the results may not be applicable to the population at large.

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Clinical Review

Review of Pancreatic Trauma

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In reviewing the literature on pancreatic trauma (1,984 cases), I found that it resulted from penetrating trauma in 73% and blunt trauma in 27% of cases. Associated injuries were common (average 3.0 per patient). Increased mortality was associated with shotgun wounds, an increasing number of associated injuries, the proximity of the injury to the head of the pancreas, preoperative shock, and massive hemorrhage. High mortality was found for total pancreatectomy, duct reanastomosis, and lack of surgical treatment, with lower mortality for Roux-en-Y anastomoses, suture and drainage, distal pancreatectomy, and duodenal exclusion and diverticulization techniques. Most patients required drainage only. The preoperative diagnosis of pancreatic trauma is difficult, with the diagnosis usually made during surgical repair for associated injuries. Blood studies such as amylase levels, diagnostic peritoneal lavage, and plain radiographs are not reliable. Computed tomographic scanning may be superior, but data are limited.

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Pancreatic trauma is relatively uncommon, and, therefore, advances in the diagnosis and treatment of injury to this organ have not developed rapidly. The first report of pancreatic trauma was by Travers in 1827[1]; the diagnosis was made at autopsy. In 1903 Mikulicz was able to identify only 45 cases of pancreatic trauma reported in the literature.[2] He noted that all 20 patients not operated on died, and 18 of 25 (72%) operated on survived. He recommended a thorough exploration through a midline incision, suture of the pancreas when needed for hemostasis, and the placement of drains in all cases. In 1930 Stern reviewed cases of traumatic injury to the pancreas.[3] Of 62 reported cases, 30 were treated successfully, and 32 patients died. Treatment recommendations were essentially the same as given by Mikulicz, and he recommended "abdominal puncture" to aid diagnosis.

The role of wartime on the development of the treatment of pancreatic injuries was reviewed by Culotta and co-workers, who found reports of 5 cases from the American Civil War with an 80% mortality, 5 cases from British troops from World War I with an 80% mortality, 62 cases from World War II with a 56% mortality, and 9 cases from the Korean conflict with a 22% mortality.[4] During the Civil War and World War I, treatment was nonoperative. Mortality rates improved during World War II with the institution of operative intervention (as previously recommended by Mikulicz) and further improved during the Korean conflict owing to better treatment of hemorrhage and shock. There were a few other early reports of pancreatic surgery, some of which have made lasting contributions.

In 1929 Newton reported the successful end-to-end suture of a transected pancreas[5]; this technique is not currently recommended. In 1946 Whipple reported his techniques for duodenal resection with total or subtotal pancreatectomy.[6] Included in his report was the observation that catgut was digested by pancreatic enzymes, leading to hemorrhage, fistula formation, duodenal leaks, and peritonitis; the use of silk was recommended. Whipple's operation, including the use of silk suture, is the currently used procedure for massive pancreatoduodenal trauma. Thus, despite limited experience, some of the basic principles of successful pancreatic surgical repair were identified early in this century. Further advances were dependent on the development of the ability to better deal with hemorrhage and shock in a severely traumatized patient, with the later development of more sophisticated pancreatic surgical techniques.

Incidence and Mortality

The incidence of pancreatic trauma in patients sustaining blunt or penetrating trauma is often quoted as being 1% to 2%.[4,7-12] Jones and Shires[13] and Howell and colleagues[14] report from separate 20-year studies an increasing frequency of pancreatic injuries. Among patients with blunt and penetrating abdominal injury, the incidence of pancreatic injury has been reported by DiVincenti and associates as 1.6% during a 1951 to 1966 study[15] and by Berni and co-workers as 3.5% during a 1971 to 1981 study.[16] Thus, the incidence of pancreatic trauma in patients with abdominal injury does appear to be increasing. It is speculated that this increase is due to more frequent high-speed motor vehicle accidents and, especially, to more frequent civil violence with knives and guns. Despite the increasing incidence of pancreatic trauma, the experience of most surgeons with pancreatic trauma will be limited enough that relying on the collected data from the literature will be required to make optimal decisions regarding the treatment of an individual patient with pancreatic trauma.

A total of 17 studies involving 1,984 patients have been reviewed.[4,8,9,12-14,16-26] The studies ranged from 3 to 36 years in length, with an average of 15 years. Pancreatic injury

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
TPN = total parenteral nutrition

was the result of penetrating trauma in 73% of cases and blunt trauma in 27%. Data regarding associated injuries were available in 12 studies involving 1,606 patients. Associated injuries were common in the liver (42%); stomach (40%); major vascular system (35%); thorax (31%); colon and small bowel (29%); spleen (25%); central nervous system, skeleton, and extremities (25%); and duodenum (18%). In nine studies, from 58% to 98% of patients had one or more associated injuries, with five noting associated injuries in 90% or more of cases. From those studies reporting a full range of injuries,[8,9,14,18,23] there were 3.0 injuries per patient.

Causes of Death in Pancreatic Trauma

The mortality of patients with pancreatic trauma is affected by several factors. In 14 studies mortality was related to the mechanism of injury.[4,8,9,12,14,18–26] The mortality following shotgun wounds was 50.6%, whereas that from all other types of penetrating and blunt trauma ranged from 7.1% to 23.1%. Patients with penetrating trauma are more likely to have associated injuries. Two studies report the presence or absence of one or more associated injuries in patients with pancreatic injuries resulting from penetrating or blunt trauma[14,18]; they note that 297 of 298 patients (99.7%) with penetrating trauma and 62 of 70 patients (88.6%) with blunt trauma had associated injuries. The number of associated injuries affects mortality; four studies involving 712 patients report the mortality rate for patients with zero to one, two to three, and four or more associated injuries as 2.5%, 13.6%, and 29.6%, respectively.[8,14,19,22] Associated injuries, in fact, cause most deaths in patients with pancreatic trauma. The data from five studies wherein the cause of death in patients with pancreatic trauma was attributed primarily to either pancreatic injury or associated injuries show that of 586 patients, 134 died, 35 of pancreatic injury and 99 of associated injuries, giving a ratio of associated injury to pancreatic mortalities of 3.5 to 1.[12,16,20,21,24]

Mortality also varies with the location of the pancreatic injury. Data from four studies in which mortality was related to the location of the pancreatic injury show overall mortality rates for patients with pancreatic head, body, and tail injuries to be 21.9%, 17.7%, and 9.8%, respectively.[13,18,20,25] The presence of preoperative shock, as defined by a systolic blood pressure of less than 90 mm of mercury, has been associated with an increased mortality in patients with pancreatic injuries. In three studies of patients with pancreatic trauma, 118 of 221 patients (53.4%) with preoperative shock died, whereas 41 of 597 patients (6.9%) without preoperative shock died.[8,12,20] Many of the deaths from pancreatic trauma occur in patients with massive trauma causing early death. Graham and associates in a review of 448 patients with pancreatic trauma reported 120 deaths, 47 of which (39%) occurred within 24 hours of injury, and all were due to massive hemorrhage.[8] In a similar study, Jones reported 59 deaths in 300 patients, with 26 (44%) occurring within 24 hours.[20]

Thus, when considering the mortality of patients with pancreatic injuries in relation to type and extent of injury, several factors stand out. Both blunt and penetrating trauma have similar mortality rates with the exception of shotgun wounds, which cause more than twice the mortality of the other injuries. Patients are more likely to die of associated injuries, especially of massive hemorrhage, in the first 24 hours after injury. Preoperative shock and proximal pancreatic injuries are related to increased mortality.

The operative intervention in patients with pancreatic trauma can be related to mortality. In eight studies of 1,407 patients with pancreatic trauma, mortality was reported to be related to the type of operative procedure carried out on the pancreas.[8,9,17–20,22,26] The overall mortality was 16.8%. Total pancreatectomy and pancreatic duct reanastomosis carried high mortality rates—100% and 50%, respectively—but the number of patients was too small to make meaningful comparisons. Patients not operated on had a mortality of 89.7%—pancreatic injury being determined either at a later procedure or at autopsy. Patients undergoing pancreaticoduodenectomy with a Roux-en-Y anastomosis to the distal pancreas had a 38.2% mortality. Intermediate mortality rates were seen for suture and drainage of the pancreas (19.3% mortality), Roux-en-Y anastomoses—a single loop to the left end of the pancreas or a double loop interposed between transected segments of the pancreas (16.7% mortality)—distal pancreatectomy (14.3% mortality), and the duodenal exclusion technique (12.5% mortality). Most patients (60.8%) underwent drainage only, and they had the lowest mortality (10.9%).

Certainly the mortality is not simply related to the type of operation. Those patients requiring more extensive surgical repair have more serious injuries and a higher mortality based on injury. Patients who are candidates for simple drainage represent a different risk group from those requiring resection or a treatment of major duct injuries. Evaluations and choice of techniques will be considered further. The type of drainage of the injured pancreas affects mortality and complication rates. Two studies reported mortality rates of 11.0% and 0% following the use of Penrose and sump drains, respectively,[18,24] and four studies reported complication rates of 41.4% and 8.0% following the use of Penrose and sump drains, respectively.[12,18,24,25]

Common complications had widely varying mortality rates following pancreatic injuries. Four studies involving 910 patients relate mortality to seven common complications following pancreatic trauma.[8,20,21,24] Hemorrhage (major vascular) and hemorrhagic pancreatitis were associated with mortality rates as high as 98% and 86%, respectively; sepsis was associated with a high mortality of 58%; abscess, nonhemorrhagic pancreatitis, pseudocyst, and pancreatic fistula were associated with lower mortality rates of 30%, 29%, 17%, and 14%, respectively. Pancreatic fistula was the most commonly reported complication, as reported in seven studies.[8,9,12,14,17,20,22] Of 1,104 patients, 234 had pancreatic fistulas (21.2% incidence) and 7 required closure (3.0% of fistulas). Most fistulas closed within a month. Although mortality following pancreatic trauma is related to the primary operative treatment, the operation chosen and the resultant mortality also depend on the magnitude and type of pancreatic and associated injuries. Therefore, mortality is not simply related to the type of operative procedure. Complications associated with pancreatic trauma carry widely varying mortality rates as noted earlier. The most common complication, pancreatic fistula, is associated with the lowest mortality, usually closes spontaneously within a month, and rarely requires a second operation for closure.

Evaluating Pancreatic Trauma

Serum Amylase Level

The preoperative evaluation for patients with possible pancreatic trauma is essentially an evaluation of associated injuries because there is currently no reliable preoperative test to identify acute injury to the pancreas. The serum amylase level has long been of interest as a diagnostic test for pancreatic injury since 1943 when Naffziger and McCorkle reported elevated serum amylase values in nine patients with pancreatic trauma.[27] In several more recent studies of patients with pancreatic trauma, the serum amylase level was reported as substantially elevated in from 10% to 91% of patients who had serum amylase determinations preoperatively.[12,13,17-20,28] Olsen reported the results of serum amylase determinations obtained within 30 minutes of admission to an emergency department from 179 patients with blunt abdominal trauma.[29] He found elevations of the amylase level in 36 patients (20%). Of these 36 patients, 3 (8%) had pancreatic injury, 2 (6%) had small bowel injury, 19 (53%) had other intra-abdominal injury, and 12 (33%) had no intra-abdominal injury, leading to the conclusion that an elevated serum amylase level is not diagnostic of pancreatic trauma. Moretz and colleagues reported data from 51 patients undergoing exploratory laparotomy for blunt abdominal trauma and found no correlation between the preoperative serum amylase value and pancreatic injury.[30] Bouwman and co-workers found no additional diagnostic accuracy of the serum amylase level when isoenzyme levels were used.[31] White and Benfield found that only 25% of patients with pancreatic injury had elevated serum amylase levels preoperatively (patients with elevated amylase values and no pancreatic injury were not considered); all had normal serum amylase levels in the early postoperative period, but a persistently elevated urinary amylase value was found to predict the inability of patients to tolerate feeding.[32] Thus, a serum amylase determination seems to be of little value in an acutely injured patient for the diagnosis of pancreatic injury; urinary amylase levels may be of value in postoperative patient management.

The finding of increased levels of amylase in diagnostic peritoneal lavage fluid has been suggested as possibly valuable in evaluating for pancreatic injury.[19,29] Several investigators have studied this method of diagnosis.[33-38] The studies are not directly comparable as different variables were often included. The current data indicate, however, that the presence of significant amounts of amylase in lavage fluid—more than 100 IU per liter—correlates with the presence of an intra-abdominal injury, but this finding is not specific for pancreatic injury.

Radiographic and Imaging Studies

A plain film of the abdomen may be contributory in diagnosing pancreatic trauma, primarily when associated with duodenal trauma. Several authors have noted that gas bubbles in the retroperitoneum distributed along the right psoas margin, at the perirenal fat line, or anterior to the first lumbar vertebra as seen anteroposteriorly or by a cross-table radiograph of the abdomen are indicative of duodenal injury with a likely associated pancreatic injury.[19,39,40] Robbs and Macintyre noted this finding in 6 of 18 patients (33%) with combined pancreatic injury and duodenal perforation.[41] Other indirect signs of pancreatic injury seen on plain radiographs are displacement of the stomach or transverse colon[19,42] or a general "ground-glass" appearance developing as a later finding.[39] An upper gastrointestinal series using water-soluble contrast material has been suggested by both Balasegaram and Lucas to confirm duodenal injury suspected from plain radiographs[19,39]; in particular, these films may show perforation of the duodenum. In general, abdominal radiographs are only occasionally of value in the preoperative diagnosis of pancreatic trauma.

Computed tomography has been reported as a method of diagnosing pancreatic injury. Two initial reports discussed the diagnosis of single cases of transection of the pancreas, neither within 24 hours of injury.[43,44] Jeffrey and associates studied 300 patients with abdominal trauma using computed tomography (CT) of the abdomen; they correctly diagnosed 13 pancreatic injuries—2 contusions, 8 lacerations, and 3 pseudocysts—with 2 falsely abnormal ("false-positive") and 2 falsely normal ("false-negative") scans (both ruptures of the pancreas).[45] Cook and colleagues studied 82 patients with abdominal trauma using CT of the abdomen: 5 pancreatic injuries were identified; there were no false-negatives, 70 true-negatives, and 7 false-positives.[46] In a prospective study, 120 patients underwent CT of the abdomen for blunt abdominal trauma; two of three pancreatic injuries were diagnosed.[47] Thus, of 502 CT scans of the abdomen in three studies, the accuracy was 97.6% in diagnosing or ruling out pancreatic injury.[45-47] This reflects a high incidence of true-negative results coincident with the low incidence of pancreatic injuries. Among the three studies there were 23 actual pancreatic injuries—20 acute, 3 pseudocysts diagnosed later—giving 17 correctly diagnosed acute pancreatic injuries, with 3 false-negative and 9 false-positive readings. As more experience is gained with CT of the abdomen, the ability to diagnose pancreatic injuries by this method should improve, but currently the reliability of the procedure seems to be somewhat less than for diagnosing injuries to other solid viscera such as liver, spleen, and kidney.

Angiography, ultrasonography, and endoscopic retrograde pancreatography have been briefly studied as diagnostic procedures for patients with pancreatic trauma. Haertel and Fuchs found angiography useful in evaluating late complications, such as pseudocyst, but not useful in an acute situation.[48] Kaude and McInnis and Vallon and co-workers reached similar conclusions regarding the use of ultrasonography.[49,50] Gougeon, Bozymski, and Taxier and their associates all found endoscopic retrograde pancreatography to be valuable in the late (weeks to years) diagnosis of pancreatic duct obstruction or disruption.[51-53] None of these three procedures have been found useful in the preoperative evaluation of an acute injury with possible pancreatic trauma.

Exploratory Surgery

In most patients, the diagnosis of pancreatic trauma will be made at celiotomy. Signs, symptoms, and diagnostic tests leading to surgical therapy will often be positive due to associated injuries; from 56% to 98% of patients reported on from several studies had one or more associated injuries in addition to their pancreatic injury.[8,9,12-14,16-20,23-26] In isolated pancreatic injuries, especially from blunt trauma, signs of peritoneal irritation may not appear for 12 to 24 hours.[20] The finding of signs of peritonitis should be considered grounds for a surgical exploration. A delay in the appropriate surgical management of pancreatic injuries leads to a higher

mortality as reported by Bach and Frey who had three deaths in six patients in whom surgical treatment was delayed from 17 to 60 days after the initial injury, and there was a 90% mortality reported in patients in whom there was no surgical intervention.[8,19,26] The best method to identify pancreatic injury is a prompt surgical exploration, which should not be delayed for more advanced diagnostic tests. All patients with abdominal trauma who are either hemodynamically compromised or in whom signs of significant peritoneal irritation develop should be surgically explored. Hemodynamically stable patients with mild peritoneal signs or those with mental state changes that might obscure peritoneal signs—from head trauma or drug overdose—should undergo diagnostic peritoneal lavage or CT of the abdomen, and, if the findings are abnormal, proceed to an emergent celiotomy. Patients with normal findings on peritoneal lavage or CT of the abdomen should be followed up with serial physical examinations, with a second diagnostic peritoneal lavage or CT of the abdomen done in uncertain cases.[32]

Treatment Recommendations

On exploratory celiotomy, the pancreas is inspected by opening the lesser omental sac through the gastrocolic ligament, with the Kocher maneuver done to inspect the head of the pancreas and duodenum. The first evidence of pancreatic injury is usually given by the presence of an upper retroperitoneal hematoma. Bile staining giving evidence of bile duct or duodenal injury suggests a likely associated pancreatic injury. Once pancreatic injury is identified, the decision on the type of operative intervention is based on the degree of injury. Simple contusion without disruption of the capsule is treated by drainage alone; about 60% of patients are treated by drainage only. If a capsular laceration is identified, it should be repaired by sutures of nonabsorbable material, usually silk. Howell and colleagues found an incidence of pancreatic fistula of 40% in patients treated with drainage only as compared with 23% when suture repair of the capsule was done.[14] Similarly, Werschky and Jordan found a 35% incidence of pancreatic fistula following drainage only compared with 28% when capsule closure was used.[22] Thus, if there is a capsular disruption it should be repaired.

Preserving Pancreatic Function

In more severe pancreatic injuries with transection or devitalization of part or all of the pancreas, a decision regarding the resection of pancreatic tissue must be made. The amount of residual pancreatic tissue needed to maintain endocrine and exocrine pancreatic function has been investigated. In 1943 Dragstedt showed preservation of adequate pancreatic function in dogs following 80% to 90% distal pancreatectomy.[54] Child and co-workers in evaluating partial pancreatectomy for pancreatitis found 34 of 38 patients in whom diabetes mellitus developed following 95% pancreatic resection, but 8 patients undergoing 50% to 90% resection showed no pancreatic insufficiency.[55] In patients with pancreatic trauma, resection has rarely caused pancreatic insufficiency. Balasegaram noted no pancreatic insufficiency in more than 30 patients following as much as 90% distal resection.[19] Jones in a report of 56 patients undergoing distal pancreatectomy found postoperative diabetes mellitus in 3 of 8 patients undergoing 80% or greater resection.[20] Berni and associates found no endocrine or exocrine pancreatic insufficiency following a distal pancreatectomy in 20 patients.[16] Salam and colleagues, in detailed studies of three patients following pancreatoduodenectomy for trauma with pancreaticojejunostomy reconstruction to the remnant of distal pancreas, found no endocrine or exocrine insufficiency.[56] Thus, as much as 80% of the pancreas may be resected with little risk of inducing pancreatic insufficiency. Data are insufficient to comment on pancreatic resection in patients with preexisting diabetes. For distal resections, resecting to the left of the superior mesenteric vessels is within safe limits. Because a normal pancreas measures about 12 to 15 cm in length,[20] 80% resection would involve 10 to 12 cm of the pancreas.

The pancreas may be transected, particularly in blunt trauma, by compression against the vertebral column, producing two viable segments. Jones and Shires first described a Roux-en-Y anastomosis to both ends of a transected pancreas in 1965, reporting the case of one patient at this time.[57] In a follow-up report, Jones reported an accumulated experience with six patients with only one death due to nonpancreatic complications.[20] The author recommended this procedure only if a distal resection would require greater than 80% resection. In cases where resection of the distal transected end of the pancreas would require less than 80% resection, a distal pancreatectomy should be chosen because it is faster and avoids jejunojejunostomy and pancreaticojejunostomy anastomoses. Currently Shires, who has had experience with more than 20 additional cases of this type, recommends a Roux-en-Y interposition only when greater than 80% resection would be required, constructed with the open end to the proximal pancreatic segment, an antimesenteric enterotomy to admit the distal pancreatic segment, and a single layer of nonabsorbable sutures at both anastomoses (G. T. Shires, MD, oral communication, October 1988). He notes that this is an uncommonly required procedure not to be undertaken lightly by surgeons with limited experience in pancreatic operations.

The distal pancreatectomy should be used for patients with transection of the pancreas as just discussed and for patients with devitalization of the distal pancreas. About 25% of 1,407 patients were treated with a distal pancreatectomy with a mortality of 14%.[8,9,17-20,22,26] When doing the distal pancreatectomy, it is recommended that the stump of the pancreatic duct be identified and ligated[20] and that nonabsorbable sutures be used throughout,[6,20] with the cut end of the pancreas closed using mattress sutures.[20] An alternative to routine sutures was first reported by Andersen and coworkers, who described the use of the TA-55 Autosuture Stapler (United States Surgical Corporation, Stamford, Connecticut) for distal pancreatectomy in two patients with good results.[58] Fitzgibbons and associates reported on the results of distal pancreatectomies in 56 patients in whom suture repair was used in 27 and staples used in 29; there were no deaths due to pancreatic complications, and the postoperative morbidity was comparable in the two groups.[59] In all cases, it is recommended the cut end of the pancreas be drained. The distal pancreatectomy most frequently will require a concomitant splenectomy.[60] The distal pancreatectomy should be considered the procedure of choice for an injured distal pancreas. Greater than 80% resection should be carried out when necessary, rather than leaving behind devitalized pancreatic tissue; should pancreatic insufficiency develop, it can be controlled with the use of insulin and pancreatic enzymes, although a small rim of residual pancre-

atic tissue may prevent "brittle" diabetes from developing.[56] Splenic preservation has become a consideration with the recognition of the overwhelming postsplenectomy infection syndrome. Distal pancreatectomy with splenic preservation has been reported.[61] Pending more experience and more definitive data, surgeons must consider the relative risks of the syndrome from splenectomy versus splenic salvage, the added operative time, and possible late complications such as splenic vein thrombosis.

For more extensive injuries to the pancreas where the head or entire pancreas is devitalized, the surgical treatment is more complex. Because the head of the pancreas and the duodenum share a common blood supply, the two must be resected together. Total pancreatoduodenectomy is rarely used; among 1,407 patients,[8,9,17-20,22,26] this treatment was used in only 1 case (0.07%) reported by Graham and colleagues, and this patient died.[8] There has been more experience with pancreatoduodenectomy with Roux-en-Y anastomosis to a preserved remnant of distal pancreas. This was carried out in 34 of the 1,407 patients (2.4%) with a 38% mortality. Preserving the distal pancreas has the advantage of leaving functional pancreatic tissue to support endocrine and exocrine function, but it does add operative time to complete the construction of the Roux-en-Y anastomosis in a patient who most likely has substantial associated injuries. On the other hand, preserving adequate pancreatic function may be an important factor in the postoperative nutrition of the patient with effects on short- and long-term recovery. In a review dealing solely with pancreatoduodenectomy, Lowe and co-workers found a mortality of 30% among all cases reported in the literature.[60] They identified six cases in which the distal pancreas was sutured without reestablishing the continuity of the intestinal tract; three of these patients died, and pancreatic fistulas developed in the other three. In 37 patients in whom pancreaticointestinal continuity was restored, 7 (19%) died and fistulas developed in 2 (6% of survivors). They recommended end-to-end choledochojejunostomy, antrectomy with gastrojejunostomy, and vagotomy as other aspects of the procedure. The experience with pancreatoduodenectomy with Roux-en-Y anastomosis to the distal pancreas versus the total pancreatoduodenectomy for trauma is presently too limited to make definitive statements regarding the procedures of choice. When faced with devitalization of the head of the pancreas and the duodenum requiring resection of these structures, a surgeon will need to decide whether the patient is stable enough to proceed with a construction of the Roux-en-Y anastomosis, but this would seem preferable if possible. Total destruction of the pancreas leaves total resection as the only option.

In cases where there is damage to the head of the pancreas and duodenum, alternatives to pancreatoduodenectomy have been proposed. Duodenal "diverticulization" for combined pancreatic and duodenal injury was first proposed by Berne and colleagues in 1968.[62] The operation consists of duodenal perforation repair, antrectomy, end-tube duodenostomy, gastrojejunostomy, and drainage. In a follow-up report, Berne and associates described 50 cases of duodenal diverticulization for combined pancreatic and duodenal injury with a 16% mortality; all duodenal fistulas at the site of a tube duodenostomy closed spontaneously.[63] Also noted as additions to the procedure were choledochojejunostomy (preferred) or cholecystojejunostomy if the biliary tree was injured and truncal vagotomy to minimize the risk of erosive gastritis. The method of duodenal diverticulization has also been used by Proctor and Peacock with satisfactory results.[7]

A second method of treating combined pancreatic and duodenal injuries, the pyloric exclusion technique, was reported by Vaughan and co-workers.[64] The technique consists of repairing the duodenal and pancreatic perforations, oversewing the pylorus with chromic catgut sutures through a gastrotomy in the greater curvature, a diverting gastrojejunostomy at the site of the gastrotomy, and drainage. Among 75 patients treated by pyloric exclusion, only three complications—two cases of suture line bleeding and one case of gastric outlet obstruction—were directly attributable to the technique. A total of 25 patients were studied in late follow-up with upper gastrointestinal series, and all showed passages of contrast through the pylorus. Late complications consisted of marginal ulcers in three patients (4%), two of whom required surgical therapy. The technique of pyloric exclusion has also been used by Cogbill and associates in eight patients with the modification of substituting polyglactin 910 for chromic catgut sutures; there were one death (12%), two fistulas (25%), both of which closed within 21 days, and no ulcers.[17]

The rationale behind both pyloric exclusion and duodenal diverticulization procedures is to divert the stream of gastric contents from the duodenum to allow healing and to decrease the stimulation of biliary and pancreatic secretion caused by acid stomach contents entering the duodenum. Both procedures offer the advantages of a quicker, technically easier operation, no loss of pancreatic tissue, and a lower mortality as compared with pancreatoduodenectomy. They should be used in preference to pancreatoduodenectomy in cases of combined pancreatic and duodenal injury where these structures are not devitalized.

Pancreatic Duct Repair

There have been reports of several methods of treatment of a severed pancreatic duct. In 1929 Newton reported the first case of pancreatic duct repair following transection at the neck of the pancreas due to blunt injury; the duct was reapproximated with catgut sutures and the gland ends rejoined with a strip of omentum encircling the site of transection.[5] The patient survived with no sequelae following the spontaneous closure of a pancreatic fistula that drained for three weeks. In 1959 Doubilet and Mulholland reported five unusual cases in which the pancreatic duct was transected within the body of the pancreas.[65] In one case the distal remnant was intubated and drained externally directly through the abdominal wall, and in the other four cases a stent tube was directed from the distal to the proximal pancreatic duct, through the common bile duct to the cystic duct, and drained externally—a cholecystectomy and a sphincterotomy of the sphincter of Oddi were carried out on these four patients. All five patients recovered. Also in 1959, Pellegrini and Stern treated one patient by essentially the same method used in the four cases of Doubilet and Mulholland, also with a successful result.[66] In 1967 Martin and colleagues reported on ductal repair following pancreatic transection in two children; in both cases repair was accomplished with fine silk over polyethylene stent tubes with temporary external drainage from the tube, which was brought out by a transduodenal, retroperitoneal route.[67] Both children recovered, and neither had a biliary or pancreatic complication. Four of the cases reported by Doubilet and Mulholland involved a repair

two or more days after injury; in the other four of the eight cases noted earlier, treatment was carried out immediately, and the pancreatic injury was the only significant injury.

Despite the success of ductal repair in the above cases, other authors advise against ductal repair. Balasegaram attempted ductal repair by direct suture (without stenting) in four patients, leading to pancreatitis, hemorrhage, and death in two.[19] He has abandoned this treatment because he feels the procedure is too difficult and time-consuming to be used in patients with severe associated injury, and the complication rate is too high. This view is shared by Stone and coworkers.[24] Although the objections regarding the difficulty and additional operative time are valid, the fact that Balasegaram did not use stenting may have substantially affected his results. A more generally applicable view regarding ductal injury is presented by Heitsch and associates, who described the results of treating 24 patients who had distal duct injuries and 15 patients with proximal duct injuries.[21] There was a 50% (four of eight) pancreatic-related mortality in the patients with distal duct injuries treated by drainage only and no deaths in 16 patients with distal duct injuries treated with distal pancreatectomies. They recommend distal pancreatectomy for any "suspected" or confirmed distal duct injury—that is, an injury that would require an 85% or less distal pancreatectomy—with duct injury determined by clinical evidence, such as direct visualization of a duct injury, complete transection of the pancreas, central pancreatic perforation, or severe pancreatic maceration. Of the 15 patients with proximal duct injuries, 2 died of pancreatic complications following pancreatoduodenectomy; following drainage only, 7 died of pancreatic-related sepsis, 5 had pancreatic-related septic complications but survived, and 1 had an uncomplicated course. For proximal pancreatic duct injuries they recommend pancreatoduodenectomy only for extensive devitalization of the head of the pancreas or duodenum or both; these are patients who have massive injury and a higher mortality proportional to their injury. Otherwise, they suggest individualized considerations of the use of a Roux-en-Y anastomosis to both ends of the pancreas following excision of the damaged segment, a proximal pancreatojejunostomy following a distal resection of as much as 95%, or duodenal diverticulization. Except for duodenal diverticulization, these techniques are unnecessarily complicated and probably should not be used. As an aid to the diagnosis of pancreatic duct injury, Berni and colleagues have described a method of intraoperative pancreatography wherein the pancreatic duct is intubated at either the ampulla of Vater by a duodenostomy or at the cut end of the distal pancreas.[16] By using this method, they were able to reduce the incidence of pancreatic complications from 55% to 15%.

Although primary pancreatic duct repair seemed to show promise from several reports before 1970, this procedure has generally fallen into disfavor, mainly for the reasons noted by Balasegaram.[19] Indeed, the complexity and time required for ductal repair would seem to add considerable risk to patients with pancreatic trauma, most of whom have major associated injuries. Further, salvaging remnants of the distal pancreas by duct repair had little to offer because even major pancreatic resections rarely produce functional impairment. Thus, duct injuries must be identified so they are not undertreated by simple drainage. They should not be overtreated by unwarranted attempts at preserving pancreatic tissue (such as a Roux-en-Y anastomosis to both segments or by duct repair). Distal resection with preservation of some proximal tissue should be the procedure of choice.

Drainage Methods

The need for drainage of an injured pancreas has been recognized since Mikulicz recommended the use of tampon drains.[2] As the treatment of pancreatic injuries has evolved, the superiority of the use of sump drains in decreasing morbidity and mortality has been shown.[12,18,24,25] Pancreatic injuries have a significant rate of fistula formation. The pancreatic juices draining from such a fistula may contain activated proteolytic enzymes and, therefore, may be destructive. Thus, drains are intended to gain early control of pancreatic fistulas should they develop. The details of the method of drainage are only occasionally described in the literature on pancreatic trauma. Jones and Shires have consistently recommended the use of combined sump and Penrose drain systems.[13,57] Drains were brought out either anteriorly or through the 12th rib bed. They note that drainage often did not begin for 7 to 10 days and recommended that drains be left in place 10 to 14 days. Smego and co-workers also recommend the use of combined Penrose and sump drains and suggest leaving drains in place for seven to ten days.[68] Stone and associates note the ability to collect and quantitate drainage for replacement purposes when sump drains are used.[18,24] Lucas disagrees with the majority of current authors by recommending using Penrose drains only and removing them by gradual withdrawal as soon as drainage ceases rather than routinely leaving drains for 10 to 14 days.[39] He also notes the risk of perforating a viscus from erosion by sump drains, which are usually rather stiff. An intermediate position is taken by Fitzgibbons and colleagues, who recommend sump drainage for three to five days and Penrose drainage for at least ten days.[59] As noted earlier, several studies showed some advantage of using sump drains over the use of Penrose drains only.[12,18,24,25]

A reasonable course for the management of drains following pancreatic trauma would be to place both Penrose and sump drains, with the sump drain removed early to limit the risk of erosion and the Penrose drains left long enough to establish a tract. By two weeks postoperatively, in the presence of a fistula, an adequate tract should be established so that drains will be of little value. Fistula drainage fluid should be collected in an ostomy appliance to quantitate the amount of drainage and to protect the skin surrounding the fistula opening from enzymatic digestion.

A distinction has been made between high- and low-output fistulas.[69] Both types have the same incidence of spontaneous closure. Both will require careful attention in terms of electrolyte replacement in proportion to the fistula volume. The fluid may be returned to the patient by having the patient drink it—as was done for two years by one patient treated by Doubilet and Mulholland[66]—or by a nasogastric tube. In current practice, total parenteral nutrition (TPN) is used because it may be formulated to replace the electrolyte losses, has the advantage of eliminating pancreatic stimulation caused by enteral feedings, and may speed resolution of the fistula.

There have also been some reports of speeding the closure of pancreatic fistulas of a nontraumatic origin by hormonal therapy. Pederzoli and co-workers found a significant reduction in the fistula closure time using somatostatin given by a continuous drip and TPN as compared with TPN alone,

TPN with glucagon, or TPN with calcitonin.[70] Prinz and associates with more limited data showed similar trends using a somatostatin analogue that requires only twice-a-day subcutaneous administration.[71] Somatostatin likely will prove useful in treating pancreatic fistulas of traumatic origin, but data are currently lacking.

Summary

A discussion with recommendations for the evaluation and treatment of patients with pancreatic trauma has been presented. The individual experience of the vast majority of surgeons with pancreatic trauma will be limited due to the low incidence of pancreatic trauma. Therefore, a study such as this one using pooled data is needed to provide a data base for making optimal treatment decisions for patients with pancreatic trauma.

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Clinicopathologic Conference

Dialysis Disequilibrium Syndrome

Discussants
CHERYL P. HARRIS, MD, *and* JEANNETTE J. TOWNSEND, MD

JEANNETTE J. TOWNSEND, MD*: In June 1988, a 22-year-old woman was seen because she had had fever, chills, nausea, and vomiting for one week. She was accompanied by her father, who reported some complaints of headaches, most severe on the day before admission. Complete anuria had developed four days before admission.

She had a notable history in that she had been paraplegic since the age of 14 months due to injuries sustained in a motor vehicle accident, at which time she had undergone a thoracic spine operation. She had had no urinary complaints before the accident but afterwards had become incontinent with a described "weak bladder." She underwent an ileal conduit procedure at the age of 3 and did well until July 1978, when she presented with a *Pseudomonas aeruginosa* pyelonephritis involving her right kidney. Her serum creatinine level had risen from a baseline of 194 μmol per liter (2.2 mg per dl) to 804 μmol per liter (9.1 mg per dl). The patient underwent a right percutaneous nephrostomy without complication and was told that she may require hemodialysis in the future. She did well except for an uncomplicated recurrence of pyelonephritis.

On physical examination on admission she had a blood pressure of 101/71 mm of mercury, a pulse rate of 73, respirations 20, and a temperature of 34.9°C (94.8°F). Examination of the head and neck showed no abnormalities. The lungs were clear, and on cardiac examination she had a regular rate with a grade II/VI systolic ejection murmur heard best at the left sternal border. The back showed pronounced kyphoscoliosis; there was no costovertebral angle tenderness. An abdominal examination revealed a pink, healthy stoma in the right lower quadrant and no other abnormalities. There was an early sacral pressure sore with erythema but an intact epidermis. On neurologic examination she was alert and oriented and the cranial nerves were intact. There was a lower extremity flaccid paraplegia, with normal upper extremity strength. A distal peripheral neuropathy was present in all extremities. The lower extremities were areflexic.

Laboratory studies elicited the following values: leukocyte count 7.4×10^9 per liter with 0.58 polymorphonuclear leukocytes, 0.01 band forms, 0.29 lymphocytes, 0.07 monocytes, and 0.05 metamyelocytes; hematocrit 0.274; platelet count 174×10^9 per liter; prothrombin time 17.1 seconds; sodium 140, potassium 4.2, chloride 115, and carbon dioxide content 5 mmol per liter; blood urea nitrogen 38.9 mmol per liter of urea (109 mg per dl); glucose 8.9 mmol per liter (160 mg per dl); and serum creatinine 760 μmol per liter (8.6 mg per dl). Arterial blood gases measured while the patient was receiving two liters of oxygen by nasal cannula showed a pH of 7.0, Pco_2 17 mm of mercury, Po_2 119 mm of mercury, and oxygen saturation 0.95. A chest radiograph showed kyphoscoliosis but no acute disease. A pelvic ultrasonogram revealed no evidence of obstruction, and a loopogram showed a patent ileal conduit. Culture of the urine grew *Providencia rettgeri;* blood cultures were negative.

The patient was treated with a regimen of amikacin sulfate and piperacillin sodium. A right internal jugular Shiley catheter was placed. Hemodialysis was initiated at 6:30 PM on June 20, 1988. The dialysis bath solution consisted per liter of sodium, 139 mEq; potassium, 3 mEq; calcium, 3.5 mEq; dextrose, 200 mg; and bicarbonate, 39 mEq. The patient's blood pressure initially was 104/64 mm of mercury with a pulse rate of 76. At 7 PM her blood pressure was 104/64 mm of mercury with a pulse rate of 96. At 7:20 PM the patient was described as restless and mildly agitated and complained of nausea. At that time her blood pressure was 93/50 mm of mercury with a pulse rate of 48. At 7:55 PM the patient was administered atropine sulfate and droperidol. At 7:58 PM the dialysis was terminated, and the patient was lethargic, somnolent, unresponsive, and intermittently vomiting. At 7:59 PM her blood urea nitrogen level was 16.8 mmol per liter of urea (47 mg per dl), the serum creatinine was 300.6 μmol per liter (3.4 mg per dl), potassium was 2.5 mmol per liter, and sodium was 140 mmol per liter. Elective intubation was done at 8:30 PM, and shortly afterwards she suffered a respiratory arrest and was maintained on mechanical ventilation.

Computed tomography (CT) of the head done at 12:15 AM on June 21 revealed diffuse cerebral edema with obliteration of the cisterns without hemorrhage (Figure 1). The patient was hyperventilated and underwent venous hemofiltration at 1:30 AM. Dexamethasone was administered without an improvement in her mental state; epinephrine and dopamine hydrochloride were required to maintain her blood pressure during the hemofiltration.

By 8:00 AM on June 21, the patient had no spontaneous respirations or movements. She did not respond to painful stimuli and had minimal foot flexion with plantar stimulation. Caloric and corneal reflexes were absent; the pupils

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography
EEG = electroencephalogram

were 9 mm, fixed, and irregular. Deep tendon reflexes were equal in the upper extremities and absent in the lower extremities. An electroencephalogram revealed electrocerebral silence; a toxicology screen was positive only for cocaine, which had been used in the intubation procedure.

On June 22, a second electroencephalogram revealed electrocerebral silence, and after discussions with the patient's family, life support systems were discontinued.

Discussion

CHERYL P. HARRIS, MD*: There are several possible causes of this young woman's condition. Uremia alone, with or without the use of hemodialysis, is known to produce mental state changes such as confusion, lethargy, and possibly seizures but is not likely to cause the diffuse and severe cerebral edema seen on the CT scan. Various endocrinologic states could produce clouding of the sensorium, lethargy, and vomiting—nonketotic hyperosmolar coma with hyperglycemia, hypoglycemia, hyperparathyroidism with hypercalcemia, and hyponatremia—but her blood chemistry levels do not suggest one of these diagnoses.

Copper or nickel intoxication can produce some of the symptoms noted here, but the history is not compatible with these syndromes. One of the most likely scenarios involves the episode of hypotension and bradycardia that she sustained during hemodialysis, requiring the administration of atropine. A decrease of the systemic blood pressure may cause inadequate perfusion of the body's end-artery territories, including those of the central nervous system, leading to what are called "watershed infarcts." These infarcts will become edematous and, if severe enough, can draw sufficient edema fluid into the nondistensible compartment of the cranium and force the cerebral contents downward against the dura, which produces subfalcian herniation under the falx cerebri, transtentorial uncal herniation by compression of the brain stem against the tentorium cerebelli, and tonsillar herniation by extrusion of the cerebellar tonsils out through the foramen magnum. The time course of this phenomenon, however, is usually 48 to 72 hours, whereas the edema in this patient, as evidenced by the mental state changes and subsequent head CT scan, occurred in about 45 minutes, much sooner than acceptable for this explanation to be considered a possibility.

This patient appeared to have suffered herniation by her symptoms of coma with a loss of brain-stem reflexes and fixed and dilated pupils. Other possibilities for the production of edema severe enough to cause cerebral herniation include trauma or space-occupying lesions. The history does not include trauma, and no mass lesion was seen on the radiologic studies. The abrupt collection of blood such as would occur with the rupture of a vascular malformation or aneurysm or collections of subdural or subarachnoid blood could produce severe cerebral edema. Patients on dialysis have an increased incidence of subdural hematomas, but several factors weigh against this diagnosis. There is no description of acute headache or nuchal rigidity as would be expected in subarachnoid hemorrhage, and there was no blood seen on the CT scan. A lumbar puncture would have more definitively ruled out subarachnoid hemorrhage but could not be attempted in this woman because of the severity of the cerebral edema.

Given the patient's clinical situation, her rapid deterioration, and the fact that she was undergoing her first dialysis procedure, the most logical diagnosis is the now uncommonly seen dialysis disequilibrium syndrome.

The dialysis disequilibrium syndrome was first reported in 1962 by Kennedy and co-workers.[1] Although it was not named initially, the syndrome was described as the worsening of a preexisting mental confusion, headache, and sometimes muscle twitching, and it was thought to be due to delayed urea clearance from the cerebrospinal fluid.

The pathogenesis of the symptoms is still unclear, though there has been a great deal of research on the syndrome. Arieff and associates, who have published several articles on the subject, studied the pathogenesis of the syndrome by creating an experimental model of it.[2] They induced acute uremia in dogs and then hemodialyzed them. When one group of the dogs underwent a rapid, high-efficiency dialysis, they had gross brain swelling, elevated cerebrospinal fluid pressures, and generalized tonic-clonic seizures; this phenomenon was termed the experimental dialysis disequilibrium syndrome.

The cause of the brain swelling was originally presumed to be the difference in urea concentration between the cerebral cortex and the cerebrospinal fluid (CSF), causing an osmotic gradient.[3] Arieff and colleagues disputed this theory, as the urea concentrations were the same in all of the

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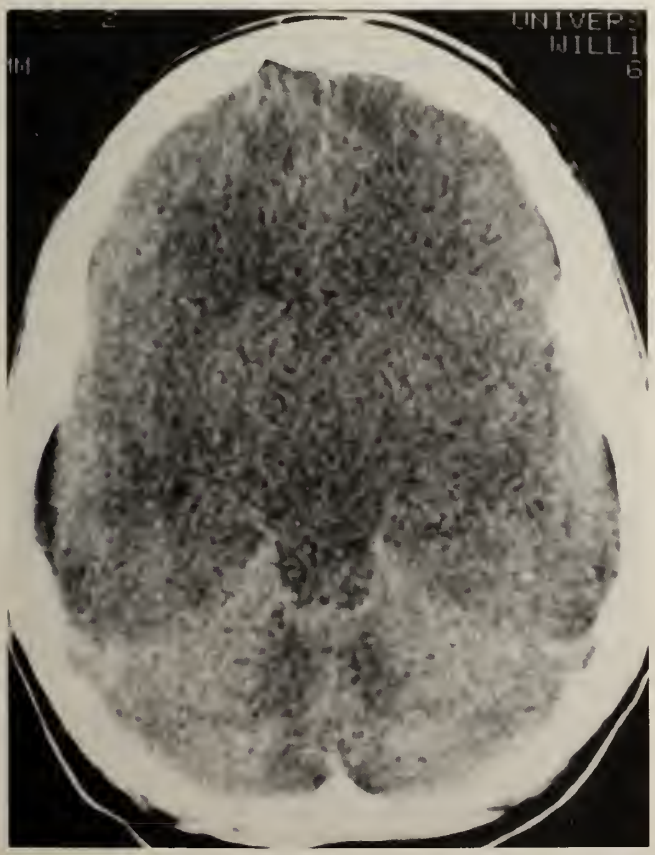

Figure 1.—An enhanced computed tomographic scan of the head shows diffuse cerebral edema.

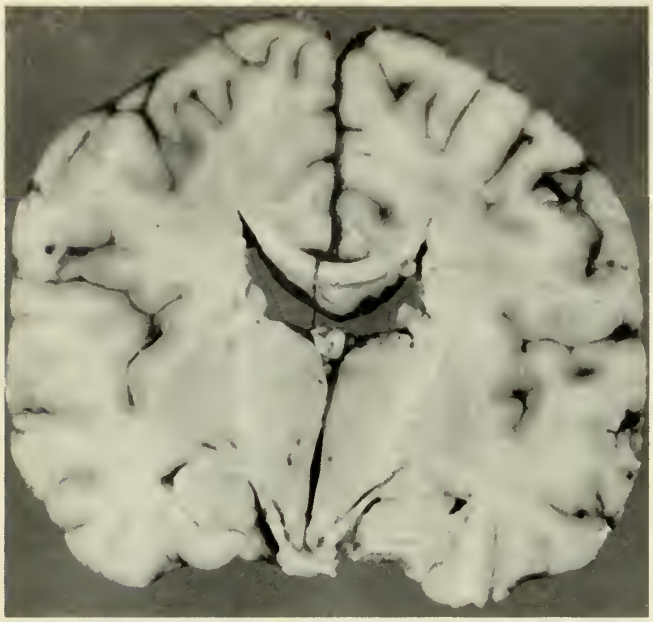

Figure 2.—A coronal section of the brain shows severe cerebral edema.

canines, but the syndrome developed in only the group that underwent rapid hemodialysis. They showed that the higher osmotic content of the brain was not related to commonly measured solutes such as sodium, potassium, chloride, calcium, urea, magnesium, or lactate. They thought, therefore, that there is a de novo generation in the brain of unidentifiable solutes that they termed "idiogenic osmoles."[2]

This increase in cerebral osmolality leads to an increase in tissue water content, or cerebral edema. This edema, described as primarily intracellular, was thought to be responsible for the symptoms of the dialysis disequilibrium syndrome.

LaGreca and co-workers (1982) evaluated the effects of hemodialysis on patients before, immediately after, and six hours after dialysis with computed tomographic scans of the head looking at "brain density."[4] They found a substantial decrease in density during and after the treatment and thought this was consistent with a postdialysis gain in cerebral water. Basile and associates (1987), however, did CT scans on patients with chronic stable uremia immediately before and after dialysis and found that brain density (by Hounsfeld units) was not affected by dialysis.[5]

An early observation was the fall in the cerebrospinal fluid pH during hemodialysis.[6] Several studies, however, support the hypothesis that the pathogenesis of the dialysis disequilibrium syndrome seems to be unrelated to changes in arterial P_{CO_2}.[3,6]

In all the articles written on the subject, the syndrome is described as almost always occurring in patients in renal failure undergoing their first hemodialysis, as in the patient presented.[6,7] Although theoretically the syndrome could develop in any azotemic patient undergoing a correction of biochemical abnormalities, it is highly unlikely to develop under any circumstances in patients with chronic stable renal failure treated with maintenance hemodialysis.[8]

Various investigators have tried manipulating the dialysate solutions with different concentrations of ingredients to attempt to decrease the incidence of the syndrome. Port and colleagues used a high concentration of sodium in the dialysate, and Rodrigo and co-workers used a high concentration of glucose.[9,10] In both reports a decrease in the incidence of the disequilibrium syndrome was claimed, but in both, patients with chronic stable uremia were studied, and the criteria for the presence of the syndrome were ill-defined.

Arieff and associates added mannitol and glycerol to the dialysis solutions.[8] When mannitol was added, cerebral edema did not occur in the dogs they were studying, using the aforementioned experimental protocol, but the electroencephalogram (EEG) of the dogs remained abnormal, and the pH of the cerebrospinal fluid decreased. When glycerol was added to the dialysate, brain edema did not occur, the pH of the CSF did not decrease, and the EEG became more normal. The authors concluded that modifying the dialysate by adding glycerol could prevent the experimental dialysis disequilibrium syndrome.

The clinical spectrum of the syndrome is broad and so diffuse that some authors consider it to be a "wastebasket diagnosis." Symptoms described in various articles include confusion, agitation, restlessness, lethargy, headache, nausea, vomiting, and muscle cramping, but seizures, coma, psychosis, and deaths have been reported.

It appears that modern methods of dialysis have altered the clinical features of the dialysis disequilibrium syndrome. Most of the seizures, coma, and deaths were reported before 1970, whereas the symptoms frequently reported during the 1980s have generally been mild, consisting of nausea, weakness, headache, fatigue, and muscle cramping.

The electroencephalogram in patients undergoing rapid hemodialysis is described as revealing bilateral bursts of high-voltage rhythmic delta waves and occasional spike and wave patterns on a high-voltage dysrhythmic background.[11] Radiologic studies directly relating to the dialysis disequilibrium syndrome have not been reported previously but should not be expected to differ much from those in the case described here, as cerebral edema is generally the neuropathologic finding.

Even though the dialysis team discontinued the procedure when the patient became symptomatic, they were unable to reverse the process of cerebral edema. Perhaps this unfortunate young woman was more sensitive to fluid and electrolyte shifts than other persons who sustain the same hemodynamic and metabolic challenges when undergoing their first hemodialysis without neurologic complications developing.

Neuropathology

Dr Townsend: At autopsy the brain weighed 1,470 grams. On external appearance it showed severe swelling with flattening of the gyri. There was evidence of bilateral tonsillar herniation with compression of the brain stem. Coronal sections showed slitlike ventricles with diffuse white matter swelling and tight sulci (Figure 2). The watershed areas between the major vessels appeared normal. There was no evidence of hemorrhage.

On microscopic examination the brain tissue was edematous with no evidence of acutely anoxic neurons. There was no evidence of infarction in a watershed distribution.

In view of the clinical course, these findings of severe cerebral edema are entirely consistent with the dialysis disequilibrium syndrome. Although acute edema is not specific for one particular disease, the lack of any trauma and the clinical course of obtundation and coma following dialysis would make these findings definitive as sequelae of the fluid shift into brain parenchyma during the dialysis procedure.

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Vibrio vulnificus Infections

THIS IS A DISEASE being seen more frequently around saltwater areas, all along the Atlantic coast, and along the Gulf coast. It is a devastating disease, an organism that is very prone to cause sepsis, shock, metastatic abscesses, and death. It does not have to be acquired through the skin; it can be acquired through ingestion. I am sure you've heard on television, if not in the journals, about the periodic cases of people who eat oysters and die. They are usually people with cancer or people on steroids or other immunosuppressive drugs. It occurs most frequently in people with bad liver disease and shunting around the liver—people with cirrhosis. If they get very sick either from the skin inoculation or from ingestion, they usually have an underlying disease. It's got to be treated quickly and have the infection removed from them and then be treated with broad-spectrum antibiotics—specifically, doxycycline—when that index of suspicion is there because of history.

—LAURENCE M. CORTEZ, MD

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Therapeutic Options in the Management of Life-Threatening Arrhythmias

Discussants
JOHN M. HERRE, MD, *and* JERRY C. GRIFFIN, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *In the past decade great advances have occurred in the diagnosis and treatment of life-threatening arrhythmias. It is becoming increasingly possible to tailor individual therapy, rather than simply to rely on trials of antiarrhythmic drugs. The principles underlying this evolving approach to cardiac arrhythmias will be reviewed by Drs Herre and Griffin of the Electrophysiology Section in the Division of Cardiology.*

JOHN M. HERRE, MD†: The development of newer antiarrhythmic drugs, surgical and catheter ablation techniques, antitachycardia pacemakers, and the automatic implantable cardioverter-defibrillator has allowed cardiac electrophysiologists to tailor therapy for the specific needs of a patient, taking into consideration age, life-style, left ventricular function, previous responses to treatment, and patients' desires regarding treatment. To illustrate these options, we will present the following case.

Case Presentation

A 22-year-old man was referred to the cardiac electrophysiology service at the University of California, San Francisco (UCSF), because of recurrent, sustained ventricular tachycardia. He had been well until three years before admission when he first presented with sustained ventricular tachycardia at a rate of 180 per minute. The tachycardia was tolerated well and was terminated by elective, direct-current cardioversion. Over the subsequent three years, he was treated unsuccessfully with β-adrenergic blocking agents, procainamide hydrochloride, quinidine sulfate, and tocainide hydrochloride. His episodes of ventricular tachycardia resulted in numerous visits to emergency departments for cardioversion. On admission to UCSF, a physical examination revealed a grade II/VI murmur at the apex. No gallops were heard, and no other abnormalities were found.

A two-dimensional echocardiogram showed a 4-cm inferoseptal aneurysm with an overall ejection fraction of 0.45. Right- and left-sided filling pressures were normal, and coronary angiography showed normal coronary arteries. An electrophysiologic study was done. Sinus and atrioventricular node function was normal. Sustained ventricular tachycardia, identical in morphology and rate to the spontaneous tachycardia, was induced with two extrastimuli.

The treatment options available included the following:

- Further drug testing, including the use of amiodarone hydrochloride, guided by programmed ventricular stimulation.
- Antitachycardia pacing.
- Automatic implantable cardioverter-defibrillator.
- Catheter ablation.
- Map-guided aneurysmectomy and endocardial resection.

Programmed Ventricular Stimulation as a Method for Evaluating and Testing Therapy in Patients With Ventricular Tachycardia

The use of programmed ventricular stimulation to reproduce and evaluate therapy for ventricular tachycardia is based on experimental evidence that suggests that the mechanism for most recurrent sustained ventricular tachycardia is reentry at the border of a scar on the endocardial surface. In the vast majority of patients, the scar is caused by a myocardial infarction. The border zone consists of nonconducting scar tissue, normal myocardium, and abnormal but viable tissue. The tachycardia originates when the trigger, usually a premature ventricular beat, enters the border zone, finds one area refractory, and conducts slowly through abnormal myocardium. The slowed conduction allows the previously refractory area to recover by the time the wave front reaches it (Figure 1). As long as the wave front does not meet refractory tissue, the tachycardia persists. Antiarrhythmic agents may alter this substrate for ventricular tachycardia either by further slowing conduction or altering the refractoriness in such a way that reentry becomes impossible or cannot be sustained.

Programmed ventricular stimulation, by creating the trigger, provides electrophysiologists with a method for

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ABBREVIATIONS USED IN TEXT

AICD = automatic implantable cardioverter-defibrillator
UCSF = University of California, San Francisco

testing the effect of an antiarrhythmic agent on the substrate for reentry. One or more electrode catheters are advanced to the right ventricle from the femoral vein to provide pacing and to record from the endocardium.

Figure 2 shows the methods used in programmed ventricular stimulation. During normal sinus rhythm, a single premature extrastimulus (S2) is introduced at twice the current required to capture the ventricle in late diastole (Figure 2-A). If ventricular tachycardia is not induced, diastole is scanned until the extrastimulus fails to capture the ventricle (Figure 2-B). Next, two extrastimuli (S2 and S3) are introduced, and diastole is scanned again (Figure 2-C). Finally, as many as three extrastimuli may be introduced either during normal sinus rhythm or after a pacing train of six to eight beats at rates of 100 to 150 per minute. Figure 2-D shows the induction of a sustained ventricular tachycardia with the use of three extrastimuli (S2, S3, and S4) following an eight-beat train at a rate of 150 per minute. Because tachycardia induction may depend on the site of stimulation and on the rate of the train of pacing, extrastimulation is carried out at two or more sites and during sinus rhythm and after pacing trains at two or more rates. Because more aggressive pacing protocols may lead to the induction of nonclinical forms of tachycardia, more than three extrastimuli or higher pacing currents are not used in our laboratory.[1]

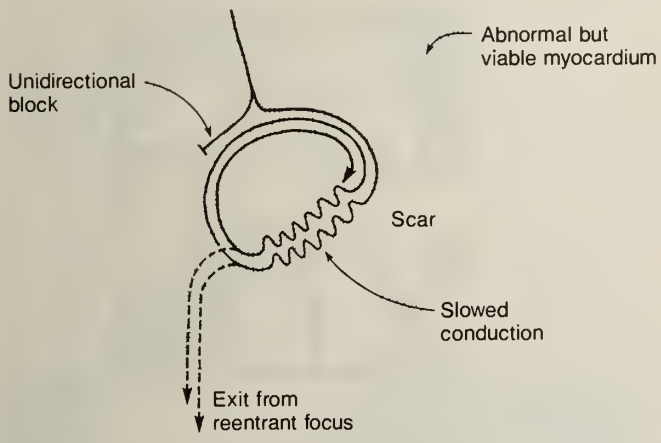

Figure 1.—The diagram shows the mechanism of reentry within an area of abnormal myocardium having heterogeneous conduction and patchy scarring. See text for details.

If ventricular tachycardia can be induced before but not after an antiarrhythmic agent is administered, then it is likely that the drug will prevent the spontaneous occurrence of the tachycardia.[2] If an induced tachycardia can be terminated reliably by pacing techniques or cardioversion-defibrillation, then it is likely that an automatic device will be successful. Finally, if the induced tachycardia is morphologically identical to the spontaneous arrhythmia and if the site of origin of the tachycardia can be located by mapping techniques, then catheter or surgical ablation is likely to prevent a recurrence of the tachycardia. Thus, the use of programmed ventricular stimulation is central to all of the options listed above.

Indications for Electrophysiologic Study in Patients With Ventricular Tachycardia

Because the likelihood of recurrence is so high, all patients resuscitated from cardiac arrest or who have had sustained ventricular tachycardia should undergo an electrophysiologic study for the selection of therapy. The high first-year mortality of patients following a myocardial infarction has led to an investigation of the use of electrophysiologic studies to evaluate the risk for sudden death in these patients. While some studies have suggested that electrophysiologic studies cannot differentiate between those patients likely to die suddenly and those likely to survive, recent studies from Australia have shown striking differences in survival between patients with and without inducible ventricular tachycardia.[3] Further studies will be needed before electrophysiologic studies can be recommended routinely following a myocardial infarction.

The usefulness of antiarrhythmic therapy for patients with asymptomatic, nonsustained ventricular tachycardia has been questioned. Electrophysiologic studies, by detecting those patients capable of sustained ventricular tachycardia, may allow an appropriate selection of patients for drug therapy. In a recent study by Gomes and co-workers, patients with good left ventricular function and no inducible sustained ventricular tachycardia had excellent prognoses compared with those with inducible ventricular tachycardia.[4] It has not yet been shown, however, that antiarrhythmic therapy alters the survival of such high-risk patients.

Finally, electrophysiologic study has been used to evaluate recurrent syncope. Particularly in patients with organic heart disease, ventricular tachycardia may cause syncope. The likelihood of a diagnostic study depends on the population studied and on the criteria used to define abnormal findings. Because these criteria vary greatly in the literature, the reported incidence of a diagnostic study ranges from 10% to

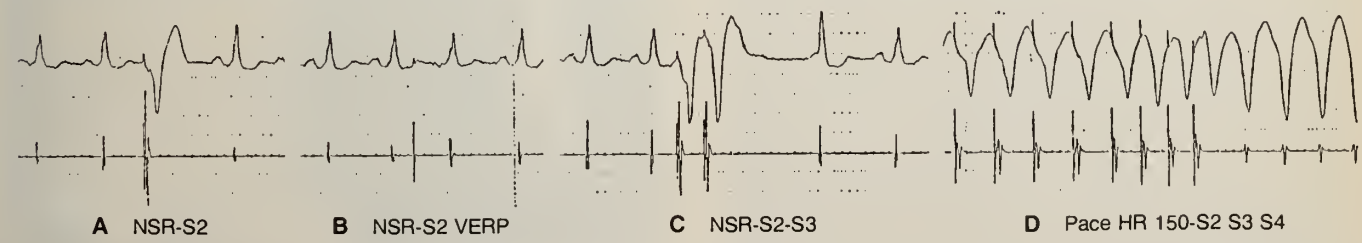

Figure 2.—These 4 panels illustrate the technique of programmed ventricular stimulation for arrhythmia induction. **A,** A single premature stimulus (S2) can be seen in both the surface electrocardiogram (top tracing) and the right ventricular endocardial electrogram (lower tracing). **B,** The premature stimulus is delivered at a cycle length sufficiently premature that it no longer is able to capture the ventricle, the ventricular effective refractory period (VERP). **C,** The initial stimulus interval has been increased just to the point of capture and a second premature stimulus (S3) added. **D,** Three premature extrastimuli are applied—S2, S3, and S4—following a period of ventricular pacing at a heart rate (HR) of 150 beats per minute. Ventricular tachycardia is seen following the last premature stimulus. NSR = normal sinus rhythm

83%.[5-7] The study is most useful in patients with organic heart disease, particularly a recent myocardial infarction, who have histories compatible with cardiac syncope and no abnormalities found on noninvasive and neurologic evaluations.

Approaches to the Treatment of Sustained Ventricular Arrhythmias

Drug Therapy

The treatment of recurrent sustained ventricular tachycardia can be approached in one of two ways. The trigger for sustained ventricular tachycardia can be attacked by attempting to eliminate or vastly reduce spontaneous ventricular premature beats, couplets, and nonsustained ventricular tachycardia observed on continuous or ambulatory monitoring. This method may be successful in patients with frequent spontaneous ventricular ectopic beats, which can be suppressed or eliminated by antiarrhythmic therapy. Many survivors of cardiac arrest, however, and patients with recurrent sustained ventricular tachycardia have only rare ventricular ectopy between episodes of sustained arrhythmia. These patients are not candidates for therapy based on ambulatory monitoring. The density of spontaneous ectopy and the degree of suppression required for a good result have not been established and validated.

Programmed ventricular stimulation allows an electrophysiologist to attack the substrate for arrhythmia. Most patients with ventricular tachycardia are treated with antiarrhythmic therapy. In general, following the induction of sustained ventricular tachycardia in a control (drug-free) state, procainamide is administered intravenously and programmed stimulation repeated. If ventricular tachycardia is rendered noninducible by intravenous procainamide, then oral procainamide or another class IA antiarrhythmic agent may be tried and programmed stimulation repeated after drug concentrations have been appropriately stabilized. If procainamide therapy fails, as it does frequently, a class IC drug such as flecainide, encainide, or propafenone or a class III drug such as sotalol (investigational) may be tried. Again, programmed stimulation is repeated after the drug level becomes stable. The trials of multiple drugs may be limited by a patient's left ventricular function. Drugs such as disopyramide, flecainide, and sotalol may worsen congestive heart failure. Drugs such as encainide and flecainide have a higher incidence of proarrhythmic effects when used in patients with poor left ventricular function.[8]

When trials of the above standard agents prove unsuccessful, amiodarone is used frequently. Its use is reserved for patients for whom other agents are unsuccessful or who are intolerant of other agents for several reasons. Because of its long half-life (about 60 days), antiarrhythmic effects are delayed, and if its use must be stopped because of ineffectiveness or intolerable side effects, elimination requires months. Side effects are common and tend to increase over time, making its use in younger patients problematic. Overall, amiodarone has little effect on left ventricular function and is frequently effective when all other agents have failed. Thus, it is used commonly in patients with poor left ventricular function and recurrent arrhythmias unresponsive to other agents.[9]

Recent evidence suggests that electrophysiologic studies may be useful in determining the prognosis of patients treated with amiodarone.[10,11] While tachycardia remains inducible in most patients, those with inducible but well-tolerated tachycardia have a better prognosis.

Despite the many antiarrhythmic agents available and the use of programmed stimulation to assess efficacy, recurrences of arrhythmia, sudden cardiac death, and intolerable side effects remain a significant problem. Fortunately, several approaches not dependent on pharmacologic therapy are now available. For the patient presented here, it seemed appropriate to pursue one of these nonpharmacologic options. The use of multiple drugs had failed clinically. With good left ventricular function and normal coronary arteries, long-term survival seemed likely if the arrhythmia could be controlled. Thus, treatment might have provided a short-term solution, but the likelihood of long-term side effects was prohibitive.

Catheter and Surgical Ablation of the Focus of Ventricular Tachycardia

To consider one of the ablative procedures, the focus of the tachycardia must be identified with sufficient precision to allow its destruction without compromising the integrity of the ventricles. This may be accomplished by ventricular mapping. In the electrophysiologic laboratory, several electrode catheters are advanced to the patient's right and left ventricles (Figure 3). The tachycardia is induced with programmed ventricular stimulation and the catheters moved about within the ventricles. Electrograms are recorded from each site and compared with the onset of the QRS complex on the surface electrocardiogram. The site where activation is earliest relative to the QRS complex is at or adjacent to the site of the origin of the tachycardia. Figure 4 shows an endocardial map generated from the patient presented here. The lines or isochrones depict the origin and propagation of the wave front on the endocardium. The tachycardia originated on the septum adjacent to the posterior wall where electrical activation began 40 ms before the onset of the QRS complex. The area with late activation corresponds to the aneurysm itself.

Armed with the catheter endocardial map, the patient was taken to the operating room. During a normothermic, partial cardiopulmonary bypass, ventricular tachycardia was induced using programmed ventricular stimulation. Using a

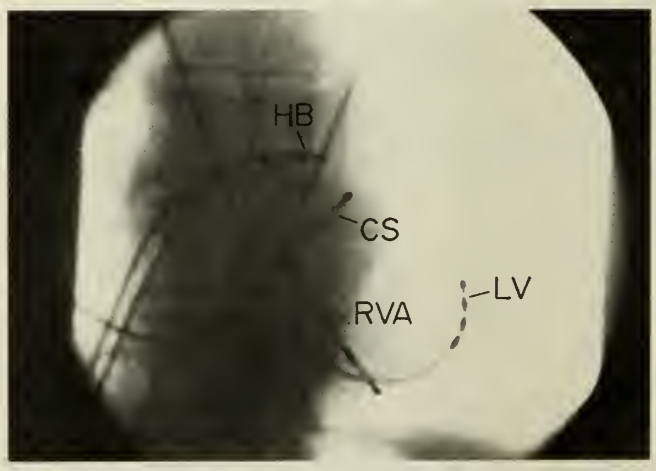

Figure 3.—The fluoroscopic image of the heart shows catheters placed for an electrophysiologic study and left ventricular mapping. Catheters are in place across the tricuspid valve near the bundle of His **(HB)**, in the coronary sinus **(CS)**, in the left ventricle **(LV)**, and in the right ventricular apex **(RVA)**.

hand-held bipolar electrode, electrograms were recorded from several epicardial sites. The isochronal map generated from the posterior portion of the heart is shown in Figure 5. Again, the site of earliest activation was adjacent to the aneurysm and corresponded to the site identified at the time of catheter mapping. Following the epicardial map, the ventricle was opened during ventricular tachycardia and the mapping repeated. The aneurysm and endocardium in the mapping-identified area of earliest activation were resected. Recently computers have been used to facilitate intraoperative mapping. Using plaques or socks with many electrodes, electrograms can be generated from many sites simultaneously, allowing complete maps to be generated from single beats during an episode of tachycardia. This significantly shortens the time required for mapping and allows mapping in patients with several morphologic types of tachycardia.

One week postoperatively, the patient was returned to the electrophysiologic laboratory and programmed ventricular stimulation repeated. Despite the use of three ventricular extrastimuli, no ventricular tachycardia could be induced. In our own and published experience, noninducibility following endocardial resection predicts an excellent outcome without the need for pharmacologic therapy. Overall results in the literature suggest an 80% success rate for endocardial resection.[12] Obviously, not all patients are candidates for open-heart operations, but endocardial resection affords an alternative to drug therapy for younger persons with preserved left ventricular function.

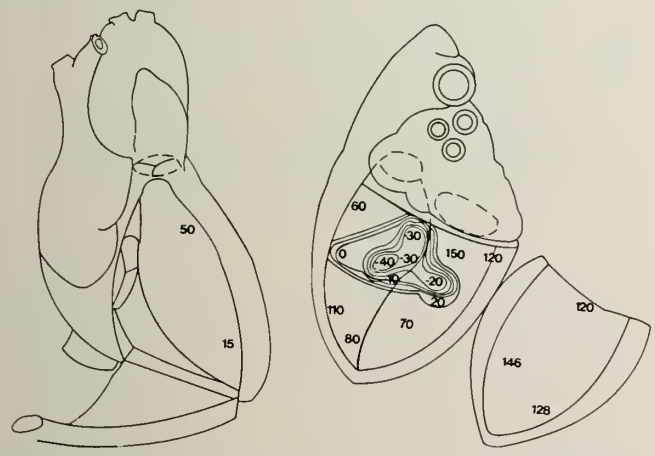

Figure 4.—The timing of activation of the endocardium is shown for both the right and left ventricles. The numbers identify isochrones of depolarization timed from the earliest beginning of a QRS complex in any standard surface electrocardiographic lead. The area of earliest activation is in the interventricular septum and occurs some 40 ms before the earliest surface Q wave.

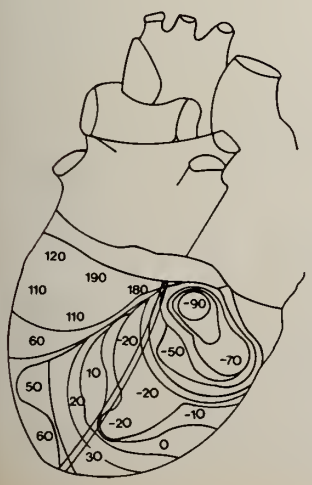

Figure 5.—This diagram shows the timing of activation of the epicardium as determined at the time of a surgical procedure. The view is of the posterior surface of the heart. The double line from base to apex represents the posterior descending coronary artery. The earliest activation occurs 90 ms before the earliest surface Q wave in an area adjacent to that identified on the endocardial map.

TABLE 1.—*Results of Catheter Ablation Worldwide**

Patients, No.	164
Follow-up duration, mo±SEM	12±11
Results	Patients, %
No ventricular tachycardia, no drugs	18
No ventricular tachycardia, taking drugs	41
Recurrent ventricular tachycardia, sudden death, or unsuccessful	34
Procedure-related deaths	7

SEM=standard error of the mean

*Data from the Percutaneous Cardiac Mapping and Ablation Registry.[16]

JERRY C. GRIFFIN, MD*: As Dr Herre mentioned, electrophysiologists, like their colleagues in the angiographic cardiovascular laboratories, have become far more interventional in the past five years. This is in large part due to ground-breaking work done here at UCSF in the early part of this decade by our colleague, Melvin Scheinman, MD. Dr Scheinman perfected the procedure now known as cardiac ablation, or fulguration.[13] The technique was originally used to block conduction at the atrioventricular junction to control the ventricular rate during a variety of atrial and supraventricular tachyarrhythmias. More recently it has been applied to foci of ventricular tachycardia and the accessory atrioventricular connections of the Wolff-Parkinson-White syndrome.[14,15] Although we are currently evaluating a number of other energy sources, including radio frequency and laser for the ablation of cardiac tissues, clinically we use the output of a standard defibrillator. This brief, high-voltage DC shock is applied either across the electrodes of a catheter inside the heart or from an electrode to a patch on the body surface. The first step in catheter ablation, as in surgical treatment, is to identify the site of earliest activation in the ventricles using mapping techniques. The center for the accumulation and maintenance of a National Institutes of Health multicenter international registry for catheter ablation for cardiac arrhythmias is here at UCSF. I will summarize the most recent compilation of that data, with regard to ventricular tachycardia.[16]

Data were obtained from 164 patients who had undergone catheter ablation of ventricular tachycardia. Most of the patients were men of early middle age. Although the predominant underlying problem was coronary artery disease, a significant number were patients in the same "miscellaneous" category as the patient presented here. Ablation was considered in the case Dr Herre described, but because of the nature of the aneurysm and its effect on left ventricular function, a surgical repair and resection of the aneurysm was selected. Most patients undergoing catheter ablation receive at least two shocks to the area of the arrhythmia focus. A substantial fraction receives more than two shocks, but these appear to be well tolerated. The clinical results in these patients are summarized in Table 1. In less than 20% was the ventricular tachycardia still eradicated at the time of the last follow-up visit and the patients asymptomatic off all antiarrhythmic drug treatment. Another 40% were also asymptomatic but

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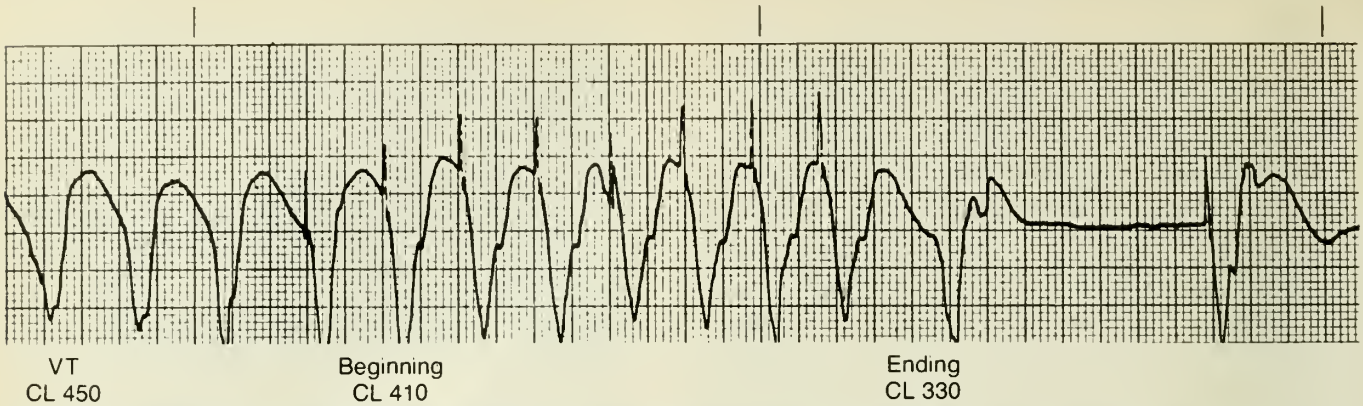

Figure 6.—This electrocardiographic strip was taken during a pacing determination of an episode of ventricular tachycardia **(VT)** of a cycle length **(CL)** of 450 ms. Pacing is initiated at a cycle length of 410 ms and decreases with each interpulse interval. By the end of the burst, the cycle length is down to 330 ms. The burst is effective, and a paced rhythm is restored.

were so only with the assistance of antiarrhythmic drugs. All of these patients had been symptomatic before the procedure because their ventricular tachycardias were not controlled when receiving the same drugs. Almost 60% of patients experienced a substantial benefit from the procedure, while 40% appeared not to have had any significant improvement. A closer examination of the patients who died during the period of follow-up shows that total cardiac mortality exceeds that of arrhythmia. These patients have advanced cardiac disease, and some die of various cardiac and noncardiac causes. There were 11 procedure-related and 16 sudden deaths in the group, presumed to have resulted from recurrent ventricular arrhythmias. So the procedure, while frequently beneficial and certainly an alternative to surgical ablation, is not a magical cure for this malignant process.

We may also take a completely different approach to the problem of sudden death through the use of device therapy for the management of these patients. At present, this might be more accurately categorized as an adjunct therapy or safety net for a more primary therapy such as drugs, surgical treatment, or ablation. Various strategies are available including arrhythmia termination, principally by defibrillation. Pacing, especially short bursts of rapid pacing, can be effective (Figure 6), but the risk of arrhythmia acceleration is substantial. Attempts to terminate a tachycardia using a burst of rapid ventricular pacing can destabilize the reentry circuit and produce a much faster and more unstable rhythm.[17] If this occurs in a patient with an implanted device, death may result. Specifically, Naccarelli and colleagues found almost 20% of patients to have arrhythmia acceleration.[17] Therefore, without an implanted defibrillator for a backup, we generally do not use automatic pacemakers in patients with ventricular arrhythmias.

Figure 7 was taken from a Holter monitor of an ambulatory patient and shows the action of the automatic implantable defibrillator in a patient with sustained ventricular tachycardia. The device is equally effective in patients with ventricular fibrillation. The present version of the implanted defibrillator is large, weighing 250 grams, and is connected to the heart using an epicardial patch electrode. On sensing ventricular tachycardia, which takes about 10 to 30 seconds, the device will deliver a sequence of four defibrillating pulses, the first of about 25 J, with three subsequent shocks of 30 J each. If the arrhythmia continues despite the delivery of these four shocks, the device becomes quiescent. It then resumes its function until after it has sensed about 30 seconds of normal rhythm. The device is triggered by the cardiac rate, and the available rate cutoffs range from 155 to 205 beats per minute. Some models also use a measure of randomness of the baseline heart rate (probability density function), which is effective for detecting ventricular fibrillation.

TABLE 2.—*Indications for Automatic Implantable Cardioverter-Defibrillator*

- Failures of diagnosis
  - No arrhythmia inducible
  - No arrhythmia on monitoring
- Inability to provide adequate preventive therapy
  - Failure of selected therapy
    - Clinical recurrence on class I drug therapy predicted effective by electrophysiologic study
    - Clinical recurrence on amiodarone therapy
    - Clinical recurrence after surgical or catheter ablation
  - Predicted high risk for failure of therapy
    - Inducible on the most effective class I antiarrhythmic drug
    - Clinical and electrophysiologic study finding predicting a high risk of failure of amiodarone therapy
    - Inducible after surgical or catheter ablation

Currently two methods of implanting the device are used. One uses a transvenous lead in the right ventricular apex and a defibrillating lead placed in the superior vena cava. This approach also requires at least one epicardial patch lead. An alternative is the use of patches on both the right and left ventricles and two epicardial screw-in sensing leads. This is the approach preferred at UCSF. A single incision is made in either the subxiphoid or the subcostal region, and the device is implanted in the abdominal wall. The device can also be implanted through a median sternotomy at the time of some other surgical procedure, such as revascularization or aneurysmectomy, or through a left lateral thoracotomy.[18]

When do we use the automatic implantable cardioverter-defibrillator (AICD)? The indications are divided into three categories (Table 2). The first is a failure to diagnose the cause of ventricular arrhythmias. Dr Herre referred to this when he talked about the patient who had recorded clinical ventricular arrhythmias but little ectopy on Holter monitoring and whose arrhythmia was not inducible in the electrophysiology laboratory. Depending on the cause of the heart disease, some 10% to 40% of patients have ventricular arrhythmia that is not inducible. This category of patients, those in whom there is no way to test the efficacy of therapy, are candidates for the AICD. The second group of patients

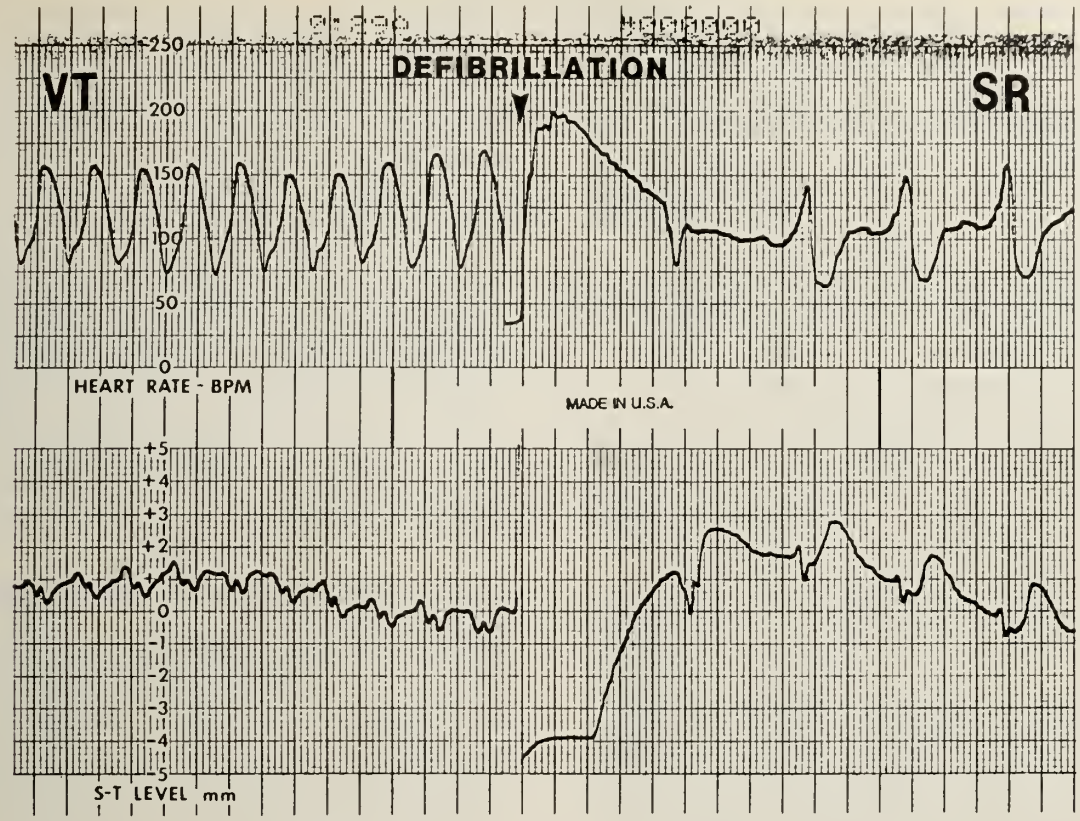

Figure 7.—This 2-channel electrocardiographic strip, taken from an ambulatory monitoring study, shows the conversion of ventricular tachycardia **(VT)** to sinus rhythm **(SR)** by a single shock from an automatic implanted defibrillator.

are those who have suffered a clinical failure of therapy with a recurrence of arrhythmia, either while taking an antiarrhythmic drug or after an operation or ablation predicted effective by electrophysiologic testing, our best predictor of therapeutic success. The final category includes those patients for whom a failure of therapy might be predicted.

We have already seen the results in patients still inducible on a regimen of class I drugs. In a study done here, we used clinical criteria to predict those patients who are at high risk despite amiodarone therapy: patients who have syncope as a presenting symptom or sudden death, those who have significant left ventricular dysfunction, and those who have persisting ventricular tachycardia on Holter monitoring after a week of amiodarone therapy.[19] An electrophysiologic study may also provide useful information about risk while on amiodarone therapy. The conversion of a hemodynamically unstable ventricular tachycardia or ventricular fibrillation to a significantly slower rhythm that is well tolerated also predicts long-term clinical success. Finally, there are those patients whose clinical arrhythmia is still inducible following surgical or ablative therapy.

Like other therapies, the AICD does not prevent progressive morbidity in these patients. They do have advanced cardiac disease, and some still die of arrhythmic and nonarrhythmic causes. What the device can do is to virtually eliminate the risk of sudden cardiac death. None of our patients have died suddenly in the first two years after implantation. As predicted from the data of Cobb and associates, empiric therapy would have resulted in an estimated 40% recurrence over the same time period.[20] Even with surgical therapy or with electrophysiologically guided drug therapy, the mortality rate is usually in the 15% to 20% range for this same time period.

There are other negatives as well. Some patients simply do not have a good psychological adjustment to this approach to arrhythmia management. A thorough discussion of the device, what it does, what it does not do, and what the expectations should be, is important in preparing patients for living with an implanted defibrillator. Patients who otherwise have a poor prognosis may not be candidates. There is a substantial morbidity, significant expense, and a small operative mortality associated with implanting the device. Finally, there are certain technical device limitations. Frequent episodes of ventricular tachycardia are not manageable with the device. First of all, the shocks are either uncomfortable—if the patient is conscious—or result in syncope. Second, the device has a limited amount of charge and a limited number of shocks that it can deliver. If the rates of ventricular tachycardia are slow and overlap with those of sinus tachycardia, unnecessary shocks may be delivered.

I will now provide a glimpse of the future. A patient was admitted to UCSF in late November 1986 with end-stage ventricular tachycardia. He had been treated unsuccessfully with eight available and investigational antiarrhythmic drugs. He had undergone a catheter ablation procedure in this hospital that was successful for a period of time in preventing the recurrence of frequent episodes, but the patient finally returned, his arrhythmia again out of control. In December 1986, he had both an AICD and an automatic tachycardia detection and terminating pacemaker implanted. In the two months after hospital discharge, he sustained 76 episodes of ventricular tachycardia, all of which were termi-

nated by the pacemaker. None of the episodes required termination by the AICD implanted in the event a pacing episode produced acceleration. The patient has continued to have ventricular tachycardia with a similar frequency, but after two years of follow-up the implanted defibrillator has been required on only one occasion. At present, the pacemaker has terminated nearly 1,000 episodes of tachycardia. We hope that in the near future we will have the capabilities of both these devices in a single pacemaker-defibrillator. At that time, the device therapy for ventricular arrhythmias can truly move into the realm of treatment rather than simply serving as a safety net.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *I have two questions regarding the paper on electrophysiologic study after myocardial infarction: First, were those patients evaluated by other known predictors of mortality after myocardial infarction, left ventricular dysfunction, and ventricular ectopic beats? Second, were they preselected as high-risk patients?*

DR HERRE: No, they were not preselected as high-risk patients. The study was a consecutive series of 175 patients. The finding of left ventricular dysfunction identified some of the same patients and some different patients as at increased risk of mortality. Ambulatory monitoring was not done in that particular study, but other studies where ambulatory monitoring has been used show that it takes a very large number of subjects to show statistically significant indices of an increased risk of mortality. So these two methods are still valid for stratifying patients following myocardial infarction. It appears that an electrophysiologic assessment may be more specific but, as you may recall, there were three studies that showed virtually no difference. The jury is still out on the value of electrophysiologic study in the postmyocardial infarction period.

PHYSICIAN IN THE AUDIENCE: *You indicated that an electrophysiologic study for patients with recurrent syncope of an unknown origin yielded about 20% diagnosable findings. Clinically speaking, how do you reconcile the separate data you mentioned earlier that in patients who have no clinical ventricular tachycardia you encounter about 2% to 10% of sustained nonclinical ventricular tachycardia—that is, a false-positive finding, depending on the number of extrastimuli used?*

DR HERRE: If you are doing a study for syncope, the end point and the interpretation of the data are a little different. A diagnostic test is one that induces a sustained arrhythmia or bradyarrhythmia, something that could have caused the patient's syncope without leading to a cardiac arrest. The nonclinical arrhythmias induced in an electrophysiologic laboratory are generally very fast, are frequently polymorphic, and frequently lead to ventricular fibrillation. The arrhythmia that we are looking for is somewhat slower, is unimorphic, and is stable. We think that we have come up with an answer that is useful in about 20% of cases.

PHYSICIAN IN THE AUDIENCE: *What are the relative costs of the different therapies?*

DR GRIFFIN: Amiodarone costs $1.50 a pill. Most patients take two pills a day, so the cost is about $100 a month. Even with follow-up visits about every six months that include a cardiogram, some lab work, and a chest radiograph, the total cost is pretty inexpensive. The cost of an electrophysiologic study is $3,000 or more. The hospital stay itself may be anywhere from a couple of days to a couple of weeks, and it is not cheap. The minimum cost of an AICD is about $25,000. The addition of an antitachycardia pacemaker costs another $10,000 and that, too, requires a couple of weeks in hospital. The cost of an arrhythmia operation is in the range of $25,000 to $40,000. So, all in all, amiodarone therapy is far cheaper than any of the things that we have talked about. Most of the methods that we talked about using are applied in patients in whom either intolerable side effects have developed or who have failed amiodarone therapy. We have few patients with defibrillators who do not fall into one of those categories. About 5% of the patients we see for ventricular arrhythmias end up with a defibrillator. So these are carefully selected patients who really do not respond to anything else.

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Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Activated Charcoal—The First-Line Agent in Cases of Overdose

THE TRADITIONAL APPROACH to overdosed patients uses charcoal as a primary adjunct following gastric emptying with ipecac-induced emesis or gastric lavage. Over the past several years, several reports suggest that charcoal may be the preferred initial and sole agent of choice in most cases of toxic ingestions. Several studies suggest that using activated charcoal alone is superior to using either ipecac alone or gastric lavage. This includes a study that showed a greater reduction in gastrointestinal absorption of a standardized dose of salicylate by giving activated charcoal and a cathartic than either ipecac-induced emesis, gastric lavage, or the use of ipecac followed by charcoal. These data, in conjunction with a consideration of the difficulties and dangers associated with gastric lavage and the physical discomfort and risks of inducing emesis, support the primary use of charcoal in cases of overdose.

Activated charcoal is formed by the pyrolysis of carbonaceous organic materials. It is activated or oxidized by passing a stream of superheated (600°C to 900°C) steam or air over its surface. The resultant material has an extremely high surface area and a high affinity for a variety of substances. Standard activated charcoal has a surface area of 950 m^2 per gram, while the newer superactivated varieties have a surface area three to four times as great.

Beyond the proven efficacy of activated charcoal in limiting the gastrointestinal absorption of toxins, there is a growing body of evidence suggesting that repeated administration may hasten the elimination of already absorbed material. The elimination half-lives of theophylline, phenobarbital, carbamazepine, digoxin, nadolol, and dapsone have all been significantly shortened by repeated dosing with activated charcoal.

The risks associated with administering charcoal are minimal. The most common and generally most serious side effect is constipation, a problem that is avoided when it is given in conjunction with a cathartic agent, such as sorbitol. Charcoal suspension is gritty, which along with its black color, makes it less than palatable. This problem can be partially overcome by mixing it with a 70% sorbitol solution and having it sipped through a straw from an opaque container.

While most agents are absorbed by charcoal, there are some notable exceptions, including hydrocarbons, malathion, carbamate, alcohols such as methanol and isopropyl alcohol, and metals like lithium and iron. Concern about the use of charcoal in cases of acetaminophen overdose has been voiced because of its potential interference with antidotal therapy with acetylcysteine. While there is evidence that acetylcysteine is absorbed by charcoal, it appears that increasing the initial dose of acetylcysteine by 30% to 40% can compensate for this problem.

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Advances in Noninvasive Diagnosis of Deep Vein Thrombosis

THE DIAGNOSIS OF DEEP VEIN THROMBOSIS on clinical grounds in an emergency department is often difficult. Contrast venography is generally considered most accurate at detecting deep venous thrombosis of the lower extremity, but its use is complicated by an allergy to contrast media and a postphlebitic syndrome in as many as 5% of patients. Noninvasive testing has traditionally relied on audible Doppler ultrasonography and leg plethysmography. In combination they show 95% of cases of acute deep vein thrombosis seen by venography. The findings in as many as 15% of patients are falsely abnormal, caused by lymphedema, obesity, old deep vein thrombosis, hematoma, or popliteal artery aneurysm.

These disorders that mimic deep vein thrombosis can now be directly viewed by high-resolution ultrasound studies using advanced high-frequency transducers. Thrombus can

be seen within the vein walls. Because organizing thrombus has a characteristic echogenicity, acute thrombosis can be distinguished from chronic thrombosis. Deep vein thrombosis is also suggested by an absence in vein compressibility by transducer-induced pressure on overlying skin. Using contrast venography as the standard, high-resolution ultrasonography is 95% sensitive and 100% specific. It is seldom used alone because of breakthroughs in Doppler scanning.

Combining high-resolution ultrasonograms with the simultaneous evaluation of blood flow through the veins by Doppler ultrasonography is called "duplex" imaging. Although traditional audible Doppler marginally increases the sensitivity of high-resolution ultrasound studies to above 95%, it cannot distinguish deep vein thrombosis in obese patients with poorly defined high-resolution ultrasound images. Computerizing the Doppler scanning makes interpreting flow less dependent on the varying expertise of technicians. Measuring the Doppler shift of a gated, pulsed wave can yield the blood velocity at a single point in a single vessel. Presented graphically, this spectral analysis of flow versus time can reveal patterns of flow characteristic of degrees of stenosis. Duplex imaging using this pulsed Doppler technique has been successful at predicting stenosis at the carotid bifurcation and flow dynamics in the heart. Duplex imaging using pulsed Doppler for deep vein thrombosis of a lower extremity shows it to be at least as sensitive as the traditional methods it will replace with increased specificities of 94% to 100% when compared with venography.

Like audible Doppler combined with plethysmography, duplex ultrasonography has a low sensitivity of 63% at revealing deep venous thrombosis limited to the calf. If this condition is to be treated, contrast venography is still indicated following a normal duplex ultrasonogram. The use of duplex ultrasonography results in fewer negative scans, however. It consistently detects disorders that mimic deep vein thrombosis such as hematoma, popliteal artery aneurysm, old deep vein thrombosis, superficial phlebectasia, and Baker's cysts missed by traditional procedures. This suggests that it has a direct contribution to the diagnosis of the cause of clinically suspected deep vein thrombosis. It can be used as an effective screening test to further reduce the need for contrast venography.

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Measuring Exhaled Carbon Dioxide in Cardiac Arrest

MEASURING THE EXHALED end-tidal carbon dioxide ($Etco_2$) content by capnography is a useful procedure for continuously monitoring the ventilation in intubated and anesthetized patients. Recently this technique has also been found to be useful in cardiac arrest, where it is used not to monitor ventilation but as an indirect measurement of pulmonary blood flow (and thus cardiac output). There has previously been no technique that could be rapidly applied to a patient in cardiac arrest to determine the actual effectiveness of cardiopulmonary resuscitation (CPR) in terms of cardiac output, cardiac index, or perfusion pressure of the heart and brain, all of which are known to be critical to the success of resuscitation and long-term recovery. Capnometry solves this problem because it is noninvasive—although patients must be intubated—and can be applied in seconds by simply placing a special adapter in-line between the endotracheal tube and the ventilating device. In patients with cardiac arrest or severe shock, $Etco_2$ measurements reflect not so much ventilation of the lungs as the delivery of carbon dioxide to the alveoli by the blood. During cardiac arrest, mixed venous CO_2 partial pressure often exceeds 100 mm of mercury because CO_2 generation by cells continues but dramatically reduced systemic circulation inhibits the elimination of gases by the lungs. (Arterial blood gas pressures at the same time may be normal and are not useful indicators of the cellular acid-base state in patients with cardiac arrest.)

Capnometry, therefore, reflects the ability of the circulation to deliver CO_2 to the lungs; in full arrest $Etco_2$ levels are often 1 to 5 mm of mercury, compared with 40 mm of mercury in patients with normal circulation. In studies of both humans and animals, the $Etco_2$ reading closely reflects cardiac output changes in 90 seconds or less. A sudden rise in the $Etco_2$ value is often the first sign of the restoration of a perfusing rhythm, before the pulse can be palpated or before changes are noted on an electrocardiographic monitor. Similarly, the $Etco_2$ level promptly reflects changes in the effectiveness of manual chest compression or the use of techniques such as interposed abdominal compression, making it possible for the first time ever to optimize CPR techniques for an individual patient to achieve the best perfusion pressures and the greatest likelihood of resuscitation. Determining the $Etco_2$ level is helpful in identifying electromechanical dissociation in patients with substantial cardiac output despite the absence of pulses or a measurable blood pressure.

The $Etco_2$ level may also have value in predicting the likelihood of a successful resuscitation. Critical coronary perfusion pressures must be achieved if a heart is to be resuscitated (and the brain preserved), and these are well correlated with the $Etco_2$ content. The ability to achieve such perfusion pressures predicts the outcome of resuscitation in animals, so it is not surprising that the $Etco_2$ level does so also. In animals, an $Etco_2$ pressure of 10 mm of mercury or more seems to be needed to achieve resuscitation, and this value is associated with a coronary perfusion pressure of 30 mm of mercury, the minimum needed for successful resuscitation. A recent study in humans found that an initial $Etco_2$ of 15 mm of mercury predicted the return of a perfusing rhythm with a sensitivity of 71%, a specificity of 98%, a positive predictive value of 91%, and a negative predictive value of 91%, independent of other factors such as the duration of resuscitation. Thus patients with pressures lower than 15 mm of mercury are highly unlikely to be resuscitated, although this still can occasionally happen. At present, clinicians can use this information as yet another indicator of the likelihood of resuscitation, like rhythm, witnessed arrest, bystander CPR, and other known predictors.

Capnography is not currently widely used in patients with cardiac arrest, but this will change as the price of the equipment decreases and clinicians learn the advantages of being able to monitor cardiac output and perfusion during an ar-

rest. Such monitoring allows changing techniques of CPR and drug dosages to optimize resuscitation for an individual patient. It also allows an early identification of inadequate perfusion in a patient despite all attempts and which patients are unlikely to benefit from further resuscitation efforts.

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Cocaine Intoxication

COCAINE CONTINUES TO BE a major drug of abuse with serious medical, public health, and socioeconomic implications. It has been estimated that 10 million people are occasional or regular users of cocaine. In 1987 there were 1,700 cocaine-induced deaths in the United States. Given its extensive use and addicting properties, medical practitioners should be prepared to recognize and treat its numerous toxic effects.

Cocaine has multiple sites and mechanisms of action that include stimulating the release and blocking the reuptake of catecholamines at specific central and peripheral nervous system neurotransmission sites. This results in excess sympathetic stimulation and increases circulating catecholamines. The contribution of the local anesthetic actions of cocaine to systemic toxic effects is unknown. The clinical effects of cocaine toxicity cover a wide spectrum. Sudden death from cocaine use has been well described and probably occurs from an acute cardiac event or seizures. Although a commonly discussed toxic effect of cocaine is on behavior, only 29.2% of patients in one study presented with an altered mental state—agitation, hallucinations, or delusions—as their chief symptom. Medical complications can commonly involve numerous organ systems and include cardiovascular collapse, myocardial infarction, chest pain, arrhythmias, syncope, seizures, headaches, asthma, abdominal pain, transient ischemic attacks, and stroke. Thus, cocaine use should be suspected in some patients when underlying causes of symptoms cannot be identified. A urine immunoassay can detect cocaine metabolites two days after use.

In recent years, the route by which cocaine abuse occurs has changed. Intravenous use has dramatically increased and has a higher potential to induce acute toxic effects. In addition, a nonion complexed form, "crack," is readily available. Unlike cocaine hydrochloride, crack when heated vaporizes and can be quickly absorbed through the lung, resulting in high serum concentrations.

The treatment of acute cocaine intoxication has been the subject of much debate. Pharmacologic agents have often been empirically selected to reverse abnormal behavior and symptoms and have not necessarily been directed toward the underlying mechanisms of cocaine toxicity. In cases of severe agitation or seizures, diazepam, 5 to 10 mg, should be given intravenously and the dose titrated to a clinical response. Clinically significant palpitations respond well to the intravenous administration of propranolol hydrochloride. Patients having myocardial ischemia should be treated with nitrates and possibly other agents and admitted to hospital. Patients who present with a hypertensive crisis should be treated with intravenous agents such as phentolamine, propranolol, or sodium nitroprusside. Labetalol hydrochloride has been used as an alternative to propranolol, but its advantages have not been clearly proved. Recent studies on animals suggest that diazepam or propranolol may be superior to labetalol or haloperidol in preventing cocaine-induced death.

The treatment of patients who have become chronically dependent on cocaine includes a supervised detoxification program. Initial trials of multiple classes of pharmacologic agents have to date identified several tricyclic antidepressants as showing promise in treating addiction in habitual cocaine users.

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HIV Disease and Emergency Medicine

EMERGENCY MEDICAL PERSONNEL at all levels need to know about and take precautions against human immunodeficiency virus (HIV) disease because they are likely to see persons with HIV infection in the course of their work and are thus at an increased risk of occupationally acquired HIV infection. The latter results from both the large number and the nature of patients typically seen in the course of emergency medicine practice and the potential for intensive and uncontrolled exposure to blood and other bodily fluids in the course of rendering emergency care.

Recent data from Johns Hopkins University Hospital (Baltimore) have shown that nearly 8% of critically ill or injured patients visiting the emergency department were infected with HIV. The actual prevalence of HIV infection among emergency department patients in western states is not well defined, but several studies in this regard are now underway.

A wide range of HIV-infected persons are likely to be cared for, at least initially, by emergency medical personnel. The most common type of HIV-infected person to be seen in an emergency department is someone who may or may not be aware of his or her HIV status but who is asymptomatic for HIV infection and has an injury or non-HIV-related illness. Other HIV-infected patients may, for various reasons, use the emergency department as their only source of care. And, of course, some will be in need of emergency care as a result of critical complications of the acquired immunodeficiency disease (AIDS). Patients may not be able to communicate information about their HIV status to emergency medical personnel or, for various reasons (including fear of discrimination), may choose not to share the information.

Recent data from California and elsewhere show that most patients with AIDS and HIV-seropositive persons continue to be from those groups generally recognized to be at high risk for HIV infection. These include homosexual and bisexual men, intravenous drug abusers, persons with hemophilia, recipients of HIV-contaminated blood, and sexual partners of all of these persons. Of the 17,164 AIDS cases

reported in California as of January 1, 1989, nearly 90% were gay or bisexual men and 4% were intravenous drug abusers.

The overall prevalence of HIV infection in western states continues to be low. For example, 0.016% of 1,550,693 units of whole blood donated in California between July 1987 and September 1988 was HIV seropositive. For the quarter ending September 1988, the HIV-seropositivity rate was 0.013%, which was down from a rate of 0.13% in the summer of 1985. Likewise, results from testing all babies born in California in July 1988 showed that only 36 of 43,301 (0.083%) had antibodies indicative of maternal HIV infection.

Data from acute care health facilities serving disproportionate numbers of higher risk persons indicate a relatively higher rate of infection. A 1987 HIV-seroprevalence survey of various types of publicly funded health facilities in 21 California counties—excluding San Francisco and Los Angeles counties—found 2.1% of 5,282 persons tested to be HIV seropositive, with the rate ranging from 1.1% in primary care public health clinics to 3.1% in sexually transmitted disease clinics. Similarly, the results of confidential HIV testing at 16 publicly funded family planning and primary care clinics from January through June 1988 showed 1.9% of 6,390 persons seropositive—0.33% of females and 6.04% of males. Further, 2.5% of 5,372 men and 3.1% of 807 women entering California's state prison system in the spring of 1988 were HIV positive. In each of these studies almost all of the seropositive persons belonged to recognized high-risk groups.

Despite the generally low prevalence of HIV infection in western states, the possibility of encountering HIV-infected persons in the course of emergency medicine practice and the consequences of acquiring the infection require that emergency medical personnel know the epidemiology and clinical manifestations of HIV disease and understand the indications for and complexities of HIV antibody testing. Emergency medical personnel also need to rigorously adhere to established infection control procedures, which assume that all patients are potentially infectious for HIV or other blood-borne pathogens.

Emergency medical personnel must assiduously guard against accidental needle sticks because they present the greatest risk for health care work-related HIV infection. To date, about 80% of all health care workers suffering work-related HIV infection have acquired the infection from needle sticks. National data indicate that the risk of acquiring HIV infection following a needle stick contaminated with blood from a known HIV-infected person is approximately 0.5%. Health care personnel have also contracted HIV infection as a result of infected blood splashing on or otherwise contacting mucous membranes or open lesions.

All emergency services should have comprehensive ongoing programs to reduce accidental needle sticks and blood exposures; training in universal body substance precautions; specified policies and procedures for voluntary and confidential HIV antibody testing of patients from whom possible exposure to HIV may have occurred, as well as for exposed workers; and a comprehensive postexposure program, including counseling and consideration of the prophylactic use of zidovudine (AZT).

All health care personnel with exposure to blood from needle sticks should be reported as soon as possible to the Hospital Infections Program at the Centers for Disease Control (CDC), telephone number 1 (404) 639-1644, for possible enrollment in a postexposure AZT study and to develop a better data base for assessing risk. A baseline blood specimen also should be drawn as soon as possible after exposure and sent to the CDC. Similarly, Burroughs Wellcome Company is enrolling participants in a placebo-controlled study of the efficacy of the prophylactic use of AZT for health care workers who have sustained a needle stick (telephone, 1-800-HIV-STIK).

Consistently adhering to universal infection control procedures and addressing other HIV-related issues and concerns may be challenging in the emergency care setting and, therefore, must be anticipated and planned for.

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Paralyzing Agents in the Emergency Department

NEUROMUSCULAR BLOCKING DRUGS have been used for many years in operating rooms to assist intubation and provide muscular relaxation. In the past five years, paralyzing agents have achieved increasing use in emergency departments and have been introduced into the prehospital care setting. Paralyzing drugs are valuable in assisting endotracheal intubation in patients with head injuries, multiple trauma, drug overdose, and status epilepticus. They are also of benefit to patients who must be rendered motionless while undergoing emergent diagnostic tests such as computed tomographic (CT) scans or invasive procedures. Recent studies support the continued use of paralyzing agents in emergency departments.

Paralyzing drugs fall into two classes. The depolarizing neuromuscular blockers cause an initial depolarization at the neuromuscular end plate, characterized by muscular fasciculations. This is followed by complete irreversible muscular paralysis within 60 seconds, which lasts 2 to 5 minutes. The most commonly used depolarizing blocker is succinylcholine chloride. The dose in children and adults is 1 to 1.5 mg per kg body weight by intravenous push.

There are a number of serious adverse effects associated with using succinylcholine, including severe bradycardia, ventricular arrhythmias, and hyperkalemia. Other complications stem from fasciculations, such as regurgitation and aspiration, displacement of fractures, new fractures in osteopenic patients, and increases in intraocular pressure. Most possible complications of succinylcholine use can be avoided by carefully screening patients and using premedication. Administering atropine sulfate will prevent bradycardia; a priming dose of a nondepolarizing neuromuscular blocker will prevent fasciculations.

The nondepolarizing muscle relaxants (NDMRs) bind to the acetylcholine receptor at the neuromuscular end plate and competitively inhibit acetylcholine. They first cause muscular weakness followed by total paralysis within two to three

minutes. Fasciculations do not occur. Paralysis lasts from 40 minutes to about 3 hours, depending on the dose and agent used. Paralysis may be reversible with the use of cholinesterase inhibitors such as neostigmine. The effects of NDMRs may be notably prolonged in patients with neuromuscular diseases such as myasthenia gravis. The NDMR drugs most commonly used are pancuronium bromide, atracurium besylate, and vecuronium bromide. Administering pancuronium (dose, 0.1 mg per kg) produces paralysis lasting about 60 minutes. The effects of atracurium (0.5 mg per kg given intravenously) and vecuronium (0.1 to 0.15 mg per kg intravenously) last 25 to 40 minutes. Vecuronium may be the ideal NDMR for emergency department use because it is short acting and causes minimal histamine release and hemodynamic changes.

Since 1986 at least four studies have been published to document the safe and effective use of neuromuscular blocking drugs in emergency departments. Emergency care physicians typically use succinylcholine to assist intubation in the subset of patients noted. The NDMR drugs are used to maintain paralysis in intubated patients and to induce paralysis in patients who have head CT scans or invasive procedures. Despite the fact that paralyzing drugs were used almost exclusively in critically ill patients in these studies, reported serious complications were rare.

There are a number of prerequisites to the efficient, safe use of neuromuscular blockers by emergency staff. First, physicians must be expert in airway management, including the rare instance when a cricothyrotomy will be necessary. Patients who might be difficult to intubate and ventilate after paralysis—that is, those with epiglottitis, massive facial trauma, or airway obstruction—are not candidates for the use of paralyzing drugs. Each of the centers reporting success and safety with paralyzing drugs mandated special training by physicians and nurses in the pharmacology and complications of neuromuscular blocking drugs. Attention was given to premedication to minimize succinylcholine side effects, careful cardiac monitoring of patients during intubation, sedation of awake patients who were paralyzed, and assuring adequate oxygenation and ventilation once paralysis occurred.

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Pulse Oximetry in Emergency Medicine

PULSE OXIMETRY is a noninvasive and continuous measurement of oxygen saturation (Sao_2). Oxygen saturation is measured by placing a special sensor on a patient's finger, toe, or nose. This sensor consists of a light-emitting diode—which projects two discrete wavelengths of light corresponding to saturated and unsaturated oxyhemoglobin—and a photodetector.

During the diastolic phase of a patient's pulse wave, a reference intensity of light is discerned. During systole the light intensity will vary with the amount of oxygenated hemoglobin present in the blood. Because the measurements are made using the change in light absorption between systole and diastole, no interference is present from anatomic aspects other than hemoglobin. Unlike its predecessor, the transcutaneous oxygen monitor, the pulse oximeter does not need to be "warmed up" or calibrated.

Oximetry was first conceptualized in the 1930s, but Leland Clark's introduction of the polarographic oxygen electrode in 1954 paved the way for the present-day use of arterial blood gas pressures and the measurement of the partial pressure of oxygen (Pao_2). In 1983 oximetry was reintroduced in the form of pulse oximetry, and the technique rapidly gained initial acceptance through the monitoring of patients during anesthesia at risk for hypoxia. Since then clinical applications have expanded dramatically and presently include all patients at risk for hypoxia—such as those with respiratory failure, asthma, and endotracheal tubes in place—who would benefit from continuous oxygen saturation monitoring. The adequacy of airway management is also aided by pulse oximetry.

Many clinical and experimental studies support the fact that the noninvasive determination of Sao_2 has an accuracy of $\pm 2\%$; values of Sao_2 in the range of 70% to 99% are comparable to invasively derived laboratory values. Oxygen saturation, however, is related to the Pao_2 by the oxyhemoglobin dissociation curve, and patients who have an Sao_2 of 90% will have a resultant Pao_2 of 60 mm of mercury. Therefore, a small drop in the Sao_2 in the range of 90% to 99% will reflect a large drop in the corresponding Pao_2. In addition, it should be remembered that pulse oximetry will be inaccurate in patients with hypothermia ($<35°C$), hypotension (<50 mm of mercury), severe vascular disease, vasopressor therapy, abnormal pigmentation of the blood (such as bilirubin), or with abnormal hemoglobin (such as carboxyhemoglobin and methemoglobin).

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Thrombolytic Therapy for Acute Pulmonary Embolism

EVEN WITH prompt treatment, acute pulmonary embolism is associated with substantial morbidity and mortality. There has been considerable confusion regarding the indications for using heparin or thrombolytic agents for treating pulmonary embolism. Recent literature has, however, helped to clarify the role for each of these therapies and has emphasized the increased use of thrombolytic agents.

Thrombolytic therapy for acute pulmonary embolism has been shown to lyse clots, normalize pulmonary artery pressures, and restore pulmonary vascular perfusion faster than heparin therapy. Despite this clinical evidence, thrombolytic therapy remains underused. Although early studies suggested no difference in mortality between patient groups receiving thrombolytic therapy or heparin, more recent literature suggests there is a particular subset of patients who are most likely to benefit from thrombolytic therapy. This includes patients with massive pulmonary embolism involving two or more lobar arteries, pulmonary embolism with hemo-

dynamic compromise, or pulmonary embolism that has not responded to heparin therapy. Death in these patients is attributed to right ventricular failure due to persistent and notably increased pulmonary vascular resistance. Because of the early death associated with acute cardiovascular compromise, rapid clot lysis is desirable. The prompt use of a thrombolytic agent may facilitate the resolution of acute hemodynamic compromise in as little as two hours and lessen the likelihood of further decompensation. In contrast, heparin therapy prevents thrombus extension but does not cause thrombolysis, which may require a number of days, and therefore it does little to reverse the hemodynamic abnormalities. Thus, the choice between heparin and thrombolytic therapy may depend on the severity of hemodynamic or pulmonary compromise caused by pulmonary embolism.

Streptokinase and urokinase are the currently approved thrombolytic agents for the treatment of pulmonary embolism. Dosing recommendations include an initial bolus of the thrombolytic agent, followed by a maintenance infusion of the agent for 12 to 24 hours. Heparin should be used after thrombolytic therapy is discontinued when the thrombin time has returned to less than twice the baseline value.

Recombinant human tissue-type plasminogen activator (tPA), although presently lacking approval of the Food and Drug Administration for the treatment of pulmonary embolism, has been an effective therapy in experimental studies. In a recent clinical trial, infusing tPA resulted in significantly earlier clot lysis than using urokinase as assessed by pulmonary angiography, with a corresponding fall in the pulmonary artery pressure not seen in the urokinase-treated patients. Thus, tPA shows promise as a second-generation therapy for pulmonary embolism.

Despite careful patient selection, hemorrhage remains a major complication of thrombolytic therapy. Minor bleeding from puncture sites may occur and can usually be controlled with pressure dressings, but if major bleeding occurs, the thrombolytic agent should be discontinued, and fresh frozen plasma may be given. In addition, febrile and mild allergic reactions are common, particularly with the use of streptokinase, and generally respond to treatment with antipyretics and antihistamines.

The incidence of serious bleeding can be reduced by careful patient selection. Thrombolytic agents are contraindicated in patients with a history of stroke, a major neurosurgical procedure within the past two weeks, or active gastrointestinal hemorrhage. Relative contraindications are many and include uncontrolled hypertension, recent gastrointestinal bleeding, coagulopathy, and recent trauma or chest compressions.

Thus, there is now considerable supportive evidence that thrombolytic therapy decreases the acute morbidity of pulmonary embolism, at least in a subset of patients. Further studies are needed to determine the optimal dose and infusion rate for these agents. Controlled studies are also needed to determine whether thrombolytic therapy compared with heparin therapy can reduce mortality and the risk of recurrence for all patients with pulmonary embolism.

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Military Antishock Garment Reevaluated

No DEVICE in medical usage generates as intense controversy as does the military antishock trouser (MAST). When intravenous access is limited by the scope of practice of the prehospital care providers, MAST can easily be applied and a patient's blood pressure improved. Despite 20 years of use, this device was not objectively evaluated as to its effect on such variables as injury scores and, more important, mortality. A study of MAST using a statistically significant number of like injuries has yet to be done, but some recent studies cast new light on its use.

One group of investigators studied a mixed population of patients with both blunt and penetrating trauma in Houston's Emergency Medical System, which has rapid response and transport times. By alternating the days in which MAST was used, they showed no difference in the prehospital times, prehospital trauma scores, the amount of prehospital intravenous fluid administered (1,200 ml), or the ultimate mortality of these trauma patients. Even in a subset of patients with severe shock, defined as those with an initial blood pressure of less than 70 mm of mercury, no difference in mortality occurred. These patients theoretically would be most likely to benefit from MAST use but did not.

Seemingly well-designed, the Houston study was heavily weighted with cases of penetrating trauma. Only 18 of 342 patients sustained blunt abdominal trauma, an important subset that cannot be independently analyzed due to the small number of patients.

In San Francisco a retrospective review of trauma patients treated with MAST compared with those in whom MAST was not available showed similar findings. Prehospital transport was not delayed and blood pressure was improved with the use of MAST, but no difference in mortality occurred. When dissecting these data for the subgroups of patients who might benefit most from MAST, it was found that those trauma victims with initial trauma scores of 4 or less uniformly did poorly despite all efforts. Those with trauma scores between 5 and 8, however, had a lower mortality with MAST use.

Critics of MAST will point to these studies as proof that using MAST is ineffective. Admittedly the strongest argument against MAST use is that it does not correct the primary injury—that of hypovolemia. Rather, it masks it with an external device that increases peripheral vascular resistance and consequently blood pressure, leading to a false sense of security by delivering an artificially normotensive patient to an emergency department. Moreover, these studies cannot be extrapolated to nonurban trauma victims where prehospital transport times are longer. Indeed, one study suggests that a subset of trauma patients may benefit from MAST use even in the urban trauma system.

While these recent studies on MAST use in an urban trauma system with transport times of 15 minutes or less cast some doubt on its benefit, MAST use is still indicated to stabilize a patient for transfer to a trauma center from a community hospital and to control pelvic fractures or retroperitoneal hemorrhage (although this, too, has not been adequately studied). Stabilizing the blood pressure with MAST

is not a substitute for adequate volume replacement in a trauma patient. Clearly, until more prospective evaluation of this device is undertaken, its use will continue to arouse controversy.

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Treatment of Near Drowning

MORE THAN 80,000 near-drowning episodes occur per year, and drowning remains the third leading cause of accidental death in the United States, claiming approximately 9,000 lives a year. Although the basic pathophysiology of near drownings is well established, the treatment of severe cases has been somewhat controversial. Recent studies help provide some answers.

The major physiologic consequences of near drowning are hypoxia, pulmonary edema, and respiratory and metabolic acidosis. Although there are mechanistic differences between seawater and freshwater, the aspiration of substantial quantities of either results in a noncardiogenic pulmonary edema with respiratory compromise. Although changes can occur in serum electrolyte levels, hematocrit, and intravascular volume, these are rarely of clinical significance.

All drowning victims should undergo an attempt at resuscitation. The primary goal of that initial resuscitation should be the immediate initiation of effective respiratory support, possibly before actual extrication from the water. Attempts to drain water from the breathing passages are generally not advisable and may increase the risk of vomiting and aspiration. Therefore, the Heimlich maneuver should not be routinely used, being reserved for those situations in which persistent airway obstruction from foreign matter is suspected or all other attempts at artificial ventilation have failed.

All near-drowning victims should be subsequently evaluated at a hospital regardless of the stability of their symptoms at the scene, although the incidence of delayed or "secondary drowning" after an asymptomatic interval appears to have been exaggerated. All patients who subsequently required admission after saltwater submersion had signs of respiratory distress within the initial four hours. Whether this is also the case for freshwater submersion remains to be established. For those patients who have considerable respiratory distress, there should be a low threshold for early endotracheal intubation and the application of positive pressure ventilation. Temperature should be checked (by the rectum) to detect major hypothermia. Complete neurologic recoveries have been achieved after more than 40 minutes of submersion in cold water in patients as old as 11 years. Therefore, resuscitation efforts in a patient with hypothermia, despite prolonged submersion, should be extremely aggressive, including a consideration of immediate cardiopulmonary bypass.

For normothermic drowning victims, the prognosis is excellent for those patients who are seen with hemodynamic stability and neurologic responsiveness. Patients requiring cardiopulmonary resuscitation and who are initially neurologically unresponsive (Glascow Coma Scale of 3 or 4) carry a poor prognosis. These patients require aggressive supportive intensive care with attention toward optimizing cardiac and pulmonary function. In addition, a number of controversial therapeutic interventions have previously been advocated in these patients. Many of these therapies, such as giving high doses of steroids, have recently been shown to have no effectiveness. While high-dose pentobarbital therapy may help to control intracranial pressure, it does not increase the number of survivors after near drowning. Although there is no doubt that patients who become hypothermic during a near-drowning episode have a better chance of surviving neurologically intact, there is no evidence that the therapeutic use of induced hypothermia increases the quantity or quality of survival. The routine use of intracranial pressure monitoring in these patients is also being questioned but will require further study. The intensive care of these patients should focus on measures to prevent further aggravation of the original cerebral injury. The key to success in the treatment of near-drowning victims is providing aggressive and effective respiratory support at the earliest opportunity.

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Hypertonic Solutions in Resuscitating Patients in Hemorrhagic Shock

TRAUMA REMAINS a major cause of morbidity and mortality; it is the leading cause of death in persons younger than 35 and the third leading cause of death in all age groups. It is estimated that half of all trauma deaths occur before reaching a hospital, many from lethal injuries that can be dealt with only by trauma prevention. Acute hemorrhage from reparable injuries is also a major cause of morbidity and mortality either owing to inadequate replenishment of the intravascular volume or from late effects of acute hypovolemia such as multiple organ-system failure.

With the introduction of trauma system planning, much has been learned regarding the initial treatment of trauma patients in both the prehospital and hospital phases. It is generally agreed that prehospital personnel contribute to patient survival by protecting the airway and the cervical spine and rapidly transporting patients to a trauma facility. Also agreed is that crystalloids—0.9% normal saline solution, lactated Ringer's mixture—are of little clinical benefit because frequently only small volumes can be infused during transport.

A growing body of evidence and experience indicates that infusing a small volume (4 to 5 ml per kg body weight) of a hypertonic saline solution (2,400 mOsm per liter) temporarily restores systemic hemodynamics as shown by increased blood pressure, cardiac output, and superior mesenteric artery flow. This effect is significantly prolonged when

dextran 70 is added to the solution. Despite its transience, this improvement in flow results in increased survival, probably by delaying some of the deleterious effects of hemorrhagic shock—such as increased lactate and myocardial depressant factor activity.

The theoretic risks of administering hypertonic-hyperoncotic solutions have not been seen clinically in humans. Bleeding abnormalities and difficulties in cross-matching due to dextran, neurologic abnormalities, clinically significant hypokalemia, and rebleeding from injured vessels have not been seen in prehospital patients given a 7.5% sodium chloride and dextran 70 solution. The administration of hypertonic (3%) saline solution reduced intracranial pressures in hemorrhaged dogs with closed head injuries and was associated with less cerebral edema than the use of standard solutions.

The use of hypertonic-hyperoncotic solutions in the early resuscitation of trauma patients appears to be a promising addition to our ability to care for the severely injured in the difficult circumstances of the prehospital environment. Further data from current clinical trials should add considerably to our understanding of their role.

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Rapid Air Transport of Critically Ill Patients

THE DOCUMENTED medical benefits of the rapid delivery of critically ill patients to definitive care available only at tertiary care facilities has led to an increased emphasis on rapid aeromedical transport. Health care provision has been regionalized in urban and rural emergency medical systems in such subspecialty areas as trauma, obstetrics and gynecology, pediatrics, and cardiology. Despite the almost uncontrolled growth of helicopter programs and concerns about expense and safety, medical literature documentation of the benefits of aeromedical transport, and the desire of tertiary centers to expand their geographic referral base, has resulted in phenomenal expansion nationwide. There are 231 medical evacuation programs operating in 46 states and the District of Columbia. These include 156 hospital-based programs and more than 60 run by either the military or state and local governments.

Although data have been conflicting, no area of helicopter transport has been more closely studied than the effects of air transport on improving survival in multisystem trauma patients. Studies have shown a statistically significant survival advantage in patients with serious injury transported from an accident scene by helicopter versus ground transport. The benefits to patient survival appear to be multifactorial, including not only rapid transport to definitive care but important therapeutic interventions such as endotracheal intubation, the transfusion of blood, and high-volume infusion.

Evolving higher standards of care for a patient sustaining an acute myocardial infarction and the small window of time in which such procedures as percutaneous transluminal angioplasty can be done or thrombolytic agents administered after an acute myocardial infarction have led to a closer evaluation of the safety of helicopter transport for cardiac patients. Despite documented increases in plasma catecholamine levels during transport, numerous studies during the past three years have found infrequent in-flight complications that were managed en route. Transient hypotension is the most common preflight and in-flight complication, followed by third-degree atrioventricular block and nonsustained ventricular tachycardia.

High-risk neonatal survival increases when delivery occurs in a perinatal center compared with survival when local delivery is followed by transfer. While many air-ambulance programs provide pediatric transportation for critically ill children, there is continued debate over the transfer of high-risk obstetric patients. A nationwide review of 315 helicopter transports of women in active labor revealed that, despite the fact that 72 were in the accelerated phase, there were no instances of in-flight delivery.

As studies increasingly define areas of possible benefit to critically ill patients, the optimal staffing of air ambulances and medical indications for air transport will be carefully delineated to further improve patient outcomes and safety in aeromedical transport.

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Update on Amphetamine Abuse

THERE HAS BEEN a disturbing increase in the illicit production and abuse of amphetamines. One of the endemic areas for this increase has been the West Coast of the United States, particularly California.

Amphetamines have become the drug of choice for adolescents in some communities. In one inpatient adolescent drug treatment unit, methamphetamine was listed as the drug of choice by about 80% of patients recently admitted. The reasons given for this preference include availability, low cost, and a longer duration of action compared with cocaine. Both oral and intravenous use are well documented in the literature. Less well documented are the users' preference to snort or smoke methamphetamine, and, as with "crack" cocaine, smoked methamphetamine is rapidly absorbed through the lungs.

Amphetamines obtained illicitly may contain D-amphetamine, methamphetamine, related amphetamine compounds such as 3,4-methylene dioxymethamphetamine, phenylpropanolamine, ephedrine, caffeine, and nonstimulant substances. Central nervous system effects may occur with minimal dosing, and an excessive amount of drug causes systemic catecholamine hyperstimulation. Amphetamines stimulate the release and block the reuptake of central cate-

cholamines such as dopamine. Although the mechanism of action is similar to that of cocaine, some sites of action differ, and the half-life of amphetamine-induced euphoria is four to eight times longer than that of cocaine. Methamphetamine can be easily synthesized from ephedrine with inexpensive equipment. The end product of this synthetic process is a white to brown powder that can be snorted, smoked, injected, or swallowed. Because the synthesis process is usually clandestine, however, the product may contain a number of impurities. Such impurities can include toxic concentrations of lead, complex organic compounds that may be carcinogenic, or numerous amphetamine-related compounds.

Symptoms of acute intoxication are variable and can include hyperexcitability, confusion, hallucinations, and tachycardia. In severe cases, seizures and occasionally death have occurred. Amphetamines may produce a state mimicking paranoid schizophrenia and induce agitation and violence. In San Diego County in 1986, 40% of all homicides were methamphetamine related; cocaine was involved in 12% to 15%. This represented a 52% increase in methamphetamine involvement over the previous year. In San Bernardino County, the number of coroner's cases involving amphetamines is twice that of cocaine. Some emergency departments treat twice as many amphetamine-related problems as those of cocaine.

The treatment of an acutely intoxicated amphetamine patient should be directed toward ensuring an adequate airway and other supportive measures. Agitation should be controlled with the use of haloperidol, and cardiovascular hyperactivity responds to propranolol hydrochloride administration. Both of these drugs have been established as effective amphetamine antagonists in studies of animals. Although other agents such as diazepam have been used with success clinically, there are no controlled studies to validate their efficacy.

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Hydrofluoric Acid Burns of the Hand

HYDROFLUORIC ACID is one of the most dangerous acids found in the workplace. Unlike other corrosives, a considerable amount of hydrofluoric acid remains undissociated when dissolved in water. In this uncharged state, it can penetrate deeply into tissues. Injury is mainly due to the interaction between fluoride and calcium, disrupting calcium-dependent processes and producing deep tissue necrosis and severe pain. This unique injury does not respond to standard burn therapy. Instead, current treatment involves applying calcium or magnesium after decontaminating by copious water irrigation. The choice of vehicle and the technique of administration depend on several factors: the surface area involved, the concentration of hydrofluoric acid, and the duration between exposure and treatment.

A minor burn is defined as an injury involving a few square centimeters of tissue (sparing the nail and nailbed), contact with a hydrofluoric acid concentration of less than 20%, and treatment soon after exposure. Treatment consists of bathing the hand in a 10% to 25% solution of magnesium sulfate and massaging the burn with a 2.5% calcium gluconate gel for at least 30 minutes. If pain persists after one to two hours of this therapy, the injured area is cautiously injected with a 10% calcium gluconate solution using a 27-gauge needle. The area infiltrated should extend 5 mm beyond the burn edge. A dose of 0.5 ml per cm^2 of involved tissue is recommended. For digital burns, no more than 0.5 ml per phalanx should be injected to avoid pressure necrosis.

A more aggressive approach is required for exposures involving hydrofluoric acid concentrations of greater than 20%, tissue contamination of more than a few square centimeters, or a long delay between contact with any concentration of hydrofluoric acid and treatment. Here, deep tissue injury is likely, and ointments or solutions cannot diffuse far enough to be effective. The initial management consists of calcium gluconate infiltration as described earlier. If the nailbed is affected, the nail must be removed before the calcium gluconate can be administered. Any bullae or necrotic tissue must be debrided.

In severe burns, those involving large areas of the hand, or if more than one nailbed is contaminated, infiltration with calcium gluconate becomes impractical. Instead, an intra-arterial infusion of calcium gluconate is the treatment of choice. A radial arterial line is established using a standard aseptic technique. Two grams of calcium gluconate are dissolved in 200 to 250 ml of a normal saline solution and infused by pump over four hours. The line is then maintained with heparinized saline for four to six hours. Should typical hydrofluoric acid pain return during this period, the patient is re-treated. After the second infusion, if avascular-appearing tissue remains, conservative debridement is carried out. This may include nail removal if the nailbed does not show improvement. This process continues until the patient is pain-free.

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Prehospital Intubation of Trauma Patients

ESTABLISHING AN AIRWAY is the foremost priority in resuscitating any acutely injured patient. Most blunt trauma victims who require airway intervention have either sustained a major head injury or have respiratory distress due to thoracic trauma or hypovolemic shock. Establishing an airway in these patients can be lifesaving by alleviating hypoxia, lowering the intracranial pressure, and preventing aspiration.

Although there has been a trend in the prehospital setting to "scoop and run" with these patients, limiting the prehospital time expended, there is evidence that airway intervention in the field may increase survivability. Unfortunately, the need for establishing an airway in the field for a blunt trauma victim poses a dilemma to prehospital care providers. Although orotracheal intubation may be lifesaving, it has

long been taught that this technique may induce or exacerbate a spinal cord injury in a patient with an unstable cervical spine.

Despite this belief, there are a number of trauma systems successfully using orotracheal intubation with "in-line stabilization" of the head and neck in blunt trauma patients both prehospital and inhospital. In-line stabilization of the neck has been proposed as a protective measure against motion of an unstable cervical spine during orotracheal intubation. Although mounting experiential evidence supports the effectiveness of the technique, there is no scientific evidence that in-line stabilization affords any protection for an unstable spine during intubation. For this reason, alternatives to orotracheal intubation are being used in many emergency medical systems nationally.

The esophageal obturator airway is the most widely used alternative that can be placed without neck manipulation and with little training. Despite years of experience, however, there is mounting evidence that as used in the field, ventilation and oxygenation are suboptimal. Both nasotracheal intubation and cricothyrotomy are being used in the prehospital setting in several major cities, but there has been little published on their practicality in that setting.

Other promising new airway adjuncts being studied include the pharyngotracheal lumen airway and the lighted-stylet guide for orotracheal intubation. Each of these appears to show promise, but, again, more clinical trials are necessary in the prehospital setting, and their effects on cervical spine mobility need to be clarified.

In the final analysis, until an effective alternative to orotracheal intubation can be developed and field tested, the risk of prolonged hypoxia, intracranial hypertension, and aspiration far outweighs the risk of inducing a spinal cord injury in these already critically injured patients. Until then, the judicious use of orotracheal intubation with in-line stabilization under tight medical control appears to be as safe and effective as any method for establishing an airway in critically injured patients in the prehospital setting.

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Editorials

Medicine in a World of Images and Perceptions

It is difficult for a profession that has been taught to think in terms of medical science and trained to use what is known of this science in daily practice to realize that "out there" it is more often the perceptions of reality rather than the true reality that are apt to govern decisions and actions. It is therefore prudent to consider the importance of perceptions. Perceptions feed on images, and we live in a world of imagery. Advertisers and politicians are aware of the relationship between images and perceptions and know that when images become perceptions, people tend to think and act in accordance with what they perceive to be true, whether it is or is not. It is also true that physicians and the medical profession have their own imagery and perceptions, and they may be less aware of these than are the media, politicians, or even a public that may seek to exploit or take advantage of them.

Perceptions may be based on fact and reality, and many are. Most physicians see themselves as hard working, honest, and dedicated to their profession and their patients, and most, though not all, are. Many physicians and much of the medical profession also now perceive of themselves as harried, harassed, and under siege by newly imposed government regulations and third party controls, by public criticism of the profession in much of the media, and even by patients who often seem to expect the impossible, and when this is not achieved, are encouraged to seek redress by a relatively unrestrained tort system that seems ready to second guess any action or lack of action by a physician. And all of this while physicians are doing what they have been trained to do and in doing so have succeeded in delivering the best medical care the world has ever known, as is evidenced by the increasing longevity of Americans, if nothing else. To physicians and the medical profession, these perceptions of themselves and others seem very real and to be based on fact.

But these are not the perceptions that much of the public and even many patients have of physicians and the medical profession. They seem to have a different view. It is almost as though they perceive us as straying from what we are supposed to be all about. To them, many physicians seem to be leaving too much of the caring role to others. Our new science is capable of doing serious harm as well as good, and everything is costing much too much. To many of a concerned public, physicians and the medical profession often seem to be perceived as circling the wagons of our profession for defense against outside attack, when festering problems may be as much within the circle as outside of it, yet seemingly ignored. While caring for patients and the public continues to be proclaimed by the profession, the public's image or impression is that protecting our special interests is what physicians and our professional associations are now really all about. Right or wrong, this perception is strengthened by such things as a news media report that physicians and attorneys were the two largest single financial contributors to the California legislators in the last election year.

There is real danger if physicians and the medical profession come to be perceived by the public as just one more special interest group, out simply to protect its own interests. Indeed, there is reason to think that some of the public already may be starting to be disabused of special interest groups, perhaps suspecting that the influence they appear to exert may not always be in the public interest. The power base of special interest groups is the money and votes they can bring to bear to influence legislation or administrative decision, and this is beginning to be seen by at least some of the public as a perversion of the political process. It remains to be seen whether or how soon special interest groups will fall into public disfavor. Were this to occur, the medical profession would then be judged by the company it was keeping.

This need not happen, however. Physicians and their professional associations can have influence far beyond that of any special interest group if they remember who they really are and show what they are really all about for all to see. In so doing, they will be seen by the public, legislators, and others, as uniquely authoritative in their science and special expertise and as uncompromising in their caring for their patients and the public. Physicians and their professional expertise are essential ingredients of modern health care, and they are at the heart of patient care. Perceptions are based on images, and images are based on performance. As a special interest group, the profession's dollars and votes are clearly limited. But if the image of physicians and their medical associations is such that they are perceived as a skilled and truly caring profession in the public interest, then in time others will supply most of the dollars and a loyal public will supply most of the votes. The need is for a public image of professional expertise in the art and science of medicine and of a genuine caring for the best interests of patients and the public. The profession and its professional organizations had best put whatever energy and resources are needed, wherever they are needed, to be sure its professional expertise be known and recognized, and to demonstrate a caring performance, one that will be understood and appreciated by patients and the public. If a perception such as this is to prevail, it must become a high priority for physicians and for their medical associations.

MSMW

Pancreatic Injury—A Taxing Problem

The collective review on pancreatic injuries elsewhere in this issue constitutes an excellent summary of the history, evolution, and current practice in the management of pancreatic trauma. I agree with most of the recommendations made.

There is no trauma that taxes the judgment of surgeons more than pancreatic injury. It is an injury that is easy to miss completely until complications ensue. At this point, when the mortality and morbidity are high, treatment options are limited.

As can be inferred from Glancy's review, there is no good way of ruling out pancreatic trauma other than by direct inspection of the pancreas. An elevated serum amylase level is at best a warning that serious abdominal trauma may have occurred. An elevated amylase is associated with significant pancreatic injury in only about a fourth of cases, and the value is normal in 75% of the cases in which severe injury has occurred. Because the pancreas is a retroperitoneal organ, peritoneal lavage would not be expected to be positive

early in the course of a major pancreatic injury, unless there has been associated disruption of the peritoneum. As noted in the review, a computed tomographic (CT) scan is often not diagnostic in the early period following injury. It is only when severe edema or hemorrhage occurs or pancreatic secretions have accumulated that the CT scan becomes obviously positive. The use of intravenous contrast may assist in recognition, but an overreliance on CT will lead to a delay in the diagnosis, particularly in the more initially benign, less disruptive injuries.

At the operation, when there is reason to suspect pancreatic injury because of blunt trauma to the epigastrium or penetrating trauma that passes in the vicinity of the pancreas, the head, body, and tail of the pancreas must be inspected. This usually requires opening the lesser sac to view the body and tail. The head of the pancreas must be inspected and a Kocher maneuver used if there is any possibility of injury. A small hematoma can restore what appears to be a normal contour of a completely divided body of the pancreas, leading to a temptation for conservative management. On the other hand, many lacerations, particularly from knife wounds, are either superficial or miss the duct and may appear to be more blatant than they actually are, resulting in overtreatment.

Regarding operative management, injuries that appear to be in the vicinity of the duct should be treated by a distal pancreatectomy up to the point of 80% resection of the pancreas. Injuries that appear superficial and that involve the proximal portion of the head should be treated by drainage. Pancreaticoduodenal injuries may on occasion require a Whipple procedure if there is evidence of devitalization of the duodenum or the head of the pancreas; otherwise, duodenal exclusion as described by Glancy is appropriate.

I do not concur with the author's recommendation that capsular repair should be done when the injury seems minor but prefer to drain the area. Should there be a missed ductal injury, a fistula would carry a lower ultimate risk than the development of a pseudocyst resulting from intrapancreatic extravasation of enzymes. I would not recommend ductal repair in the management of any injury.

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More on the Dialysis Disequilibrium Syndrome

IN PATIENTS WITH RENAL FAILURE, there are several central nervous system disorders that may occur not as a consequence of the uremic state but, rather, because of dialytic therapy. One such disorder is the dialysis disequilibrium syndrome, which can occur in patients being treated with hemodialysis.[1-3] The dialysis disequilibrium syndrome (DDS) is a clinical syndrome that can be observed in patients with renal failure following a rapid lowering of blood urea levels by dialysis therapy. From a purely mechanical and technical standpoint, it is possible to correct most of the abnormal blood chemistry values found in uremic patients to acceptable levels in much less time than is commonly done. The efficiency of hemodialysis can be increased by increasing blood or dialysate flow rates. When this is done, however, and the blood urea nitrogen level is rapidly lowered, DDS often develops. The syndrome has been reported most frequently after rapid hemodialysis but occasionally after peritoneal dialysis. Although DDS has been reported in all age groups, it is more common among younger patients, particularly children.[4] The symptoms of DDS, which characteristically occur late in the course of the dialysis procedure, may include such manifestations as headache, nausea, emesis, blurring of vision, muscular twitching, and disorientation. Seizures and coma have been reported, but it is unclear if they are actually a manifestation of DDS or are related to underlying central nervous system disease.[1,3,5] In the past decade, the original description of the dialysis disequilibrium syndrome has been expanded to include milder symptoms, such as muscle cramps, anorexia, restlessness, and dizziness.[6-8] In the original descriptions of the dialysis disequilibrium syndrome,[9] abnormal electroencephalogram findings were noted, but more recent studies have suggested that the electroencephalogram is probably unaffected by DDS.[3,10,11]

Although the syndrome has been recognized for more than 25 years,[9] the pathogenesis is still not fully understood. A rise in cerebrospinal fluid (CSF) pressure, intracellular acidosis of brain, or brain edema may all be contributory. The CSF pressure in both uremic patients and animals with experimentally induced DDS is normal. Following hemodialysis of uremic persons (or laboratory animals) with renal failure, the CSF pressure generally rises, regardless of the presence of symptoms of DDS. An elevated CSF pressure is felt by many to indicate cerebral edema, but such an increase may be secondary to an increased brain volume of either CSF or blood, or increased brain water content (cerebral edema). In experiments with animals, it has been consistently observed that the CSF pressure will increase during hemodialysis, whether or not cerebral edema is present. The most likely explanation for this phenomenon is that during hemodialysis, urea is removed more rapidly from brain and plasma than from CSF. The rate of the removal of urea from brain closely parellels its rate of removal from plasma, but the clearance of urea from CSF is delayed, which probably accounts for the formation of an osmotic gradient between CSF and plasma after hemodialysis. This osmotic gradient presumably leads to a net movement of water into the CSF, resulting in a rise in the CSF pressure that is unrelated to brain swelling.[12] The rise in CSF pressure, although not associated with brain edema, may contribute to some of the symptoms associated with DDS, such as emesis, headache, and nausea.[2,9]

In general, patients who have renal failure and are being maintained with intermittent dialysis therapy will have a predialysis arterial pH and a bicarbonate concentration that are lower than normal. Most standard dialysate solutions contain either sodium bicarbonate or a bicarbonate precursor (acetate or lactate) at a concentration of about 30 mmol per liter. Thus, hemodialysis will increase the arterial pH by adding bicarbonate to extracellular fluid. One would predict that as the arterial pH returns to normal, the arterial P_{CO_2}, which is low in patients with chronic uremia, would rise, leading to a rise in the P_{CO_2} of the cerebrospinal fluid. It has been found, however, that during, after, and between hemodialysis, the arterial P_{CO_2} does not change appreciably.[1] Thus, we would not expect the P_{CO_2} of the CSF to change either. Studies in dialysis patients have shown that during hemodialysis there is often a substantial rise in the P_{CO_2} of lumbar CSF, with a concomitant fall in its pH.[13,14] Studies in uremic dogs treated

with rapid hemodialysis have shown that, despite a rise in the pH of arterial blood, the pH of the CSF fell. It has been found (in animal models) that the decrement in the pH of the CSF is associated with a concomitant decline in the pH of the brain, and this finding is probably a major factor in the pathogenesis of the dialysis disequilibrium syndrome.[15] A fall in the pH of CSF may contribute to a depression of the sensorium, and intracellular acidosis of brain cells could result in a rise of brain intracellular osmolality. Such an increase of osmolality could lead to brain edema. Rapid hemodialysis (in laboratory animals with acute renal failure) does result in an increase of brain osmolality and cerebral edema. The cerebral edema is thus related to a decrease in the intracellular pH of the cerebral cortex, probably as a consequence of an increased production of organic acids. It has been subsequently shown (in patients) that decreasing the rate and increasing the frequency of dialysis as part of the initial therapy for acute renal failure resulted in a lessening of both the symptoms and biochemical derangements of the dialysis disequilibrium syndrome.[1,3,8,13,14]

The clinical manifestations of DDS, in its mildest form, consist only of restlessness and severe headache during or soon after hemodialysis. This is commonly followed by nausea and vomiting, often accompanied by a blood pressure elevation.[2,9] These symptoms have been accompanied by disorientation and tremors. Seizures are uncommon but have usually been of the grand mal type. Most patients will recover from these symptoms, but recovery may take several days, at which time dialysis may again be necessary. It appears that modern methods of dialysis have altered the clinical features of DDS.[8] Most reports of seizures, coma, and death appeared before 1970. The symptoms of DDS as reported in the past 15 years have generally been mild, consisting of nausea, weakness, headache, fatigue, and muscle cramps.[8] Although seizures leading to coma and death have been reported, it is unlikely that any patient ever actually died of DDS. In most if not all such cases, the patients probably died of other neurologic complications that have been associated with dialysis, such as acute stroke, subdural hematoma, subarachnoid hemorrhage, or hyponatremia.[1-3,9,14]

As suggested earlier, dialysis patients who are afflicted with headache, nausea, emesis, and seizure activity may have diseases other than DDS. In general, in patients with these disorders, mental slowness or mild stupor commonly develop, but seizures and mental obtundation may occur. It must be emphasized that at present, the dialysis disequilibrium syndrome is rare and is a diagnosis of exclusion. There is a tendency to diagnose DDS in most patients who are being treated with dialysis and in whom central nervous system signs and symptoms develop, but the diagnosis is usually incorrect. The diagnosis of DDS can be made only after excluding other central nervous system disorders, such as a ruptured intracranial blood vessel, subdural hematoma, and other disorders.[1,14]

The management of DDS can be divided into preventive modalities and therapeutic maneuvers. In several studies, this syndrome has been treated by the addition of either hyperosmotic or hyperoncotic solute (glucose, glycerol, albumin, urea, fructose, sodium chloride, mannitol) to the dialysate or by the substitution of sodium bicarbonate for sodium lactate (or acetate) in the dialysate.[1,5,7,8,13,14] The purpose of such maneuvers has been to minimize rapid alterations in the plasma osmolality or bicarbonate during dialysis. In uremic animals undergoing rapid hemodialysis, the addition of glycerol or mannitol to the dialysate prevents many of the manifestations of experimental DDS. Studies on uremic patients undergoing hemodialysis with glycerol or mannitol added to the dialysate suggest that these agents lessen the symptoms that may be associated with DDS. The substitution of bicarbonate for acetate or lactate in the dialysate appears to have little pathophysiologic rationale, unless the patient has hepatic insufficiency or acetate intolerance, but it has been reported to diminish cardiovascular instability and may prove useful in decreasing the symptoms of DDS in some patients. Recently a technique called "pure ultrafiltration" has been developed where a patient is subjected to ultrafiltration without dialysis.[16] The net result is a loss of fluid without the patient undergoing dialysis. This procedure can then be followed by conventional dialysis without ultrafiltration. The role of ultrafiltration followed by dialysis in the prevention of DDS is currently being evaluated.[16]

The technique of continuous ambulatory peritoneal dialysis is currently in use worldwide. By this technique, patients can undergo continuous low-volume peritoneal dialysis for as long as 24 hours a day,[17] with a minimum of patient discomfort. Symptoms of DDS have not been noted in patients undergoing this procedure. At present, the occurrence of DDS is largely prevented by the use of "slow" dialysis—that is, low blood flow rates with a short duration of hemodialysis at frequent intervals in those persons in whom DDS is most likely to develop. Additional therapy, in the form of hyperosmotic or hyperoncotic additives, is currently used in selected clinical situations where there is felt to be a high probability of DDS developing.

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Lip-Reading the Bedside Care Shortage

During the decade 1845 to 1855, the requirements for an MD degree from medical schools of the major eastern universities doubled from one year of training to that of two years. In that same mid-19th century decade, Florence Nightingale led the reform movement that established nursing as a suitable independent career for a person and that nurses were to be considered professionals. She ushered in the modern education of nurses. Around the turn of this century, the requirements for medical education doubled once again—to the present four years. In the decades since, medical care has continued to evolve and physician standards have continued to increase, requiring more and more subdivision of skills and tasks. Tasks that are deemed nonessential to the gathering and analysis of critical information, followed by the synthesis of a therapeutic or corrective program for a patient, have been increasingly allocated to others trained to fill those roles. Nursing itself has similarly evolved to keep pace with constantly improving medical care. Humanity has long been aware that "the times change and we change with them."

The article by Aiken elsewhere in this issue offers a commonly expressed perspective among the leadership of nursing in America about the perceived problem of the hospital nursing shortage. It demonstrates a singular difficulty in recognizing and coming to grips with the real item on this nation's agenda—the bedside care shortage in America. Though interrelated, the two issues are not identical; yet, nursing's leadership has steadfastly refused to acknowledge this, bringing dismay to some of their closest physician friends and colleagues.

In Aiken's article, the ultimate paragraph targets the registered care technologist (RCT) proposal of the American Medical Association (AMA) as illustrating the failure of physicians and nurses to develop mutually acceptable solutions to problems that "affect the professional practice of both groups." It goes on to state that "nurses primarily support and complement medical care" and then further notes that the author's proposals will pose no economic threat to physicians' income. Presumably, they should be supported on that basis. Clearly, the author's frame of reference has been only two-dimensional: the professional aspirations and the economic needs of nursing. No one says these are unimportant, but one cannot escape the fact that the needs of the patient (or public) are given no place in this equation.

Physicians, through the AMA, have for many years consistently supported our nursing colleagues in their aspirations to enhance the professionalism of what they do. Our voice has been and continues to be raised alongside organized nursing in support of higher pay for nurses, additional federal grants for nursing education, more nursing autonomy in nursing decisions, and more continuing medical education for nurses. The result has been that, in spite of the recent declines in nursing school enrollment, our nation now has more registered nurses (RNs) than ever before, with the current estimate standing at 1.9 million, of whom approximately 1.6 million are in the work force.[1] Aiken's point is that, over time, nursing duties have become more diversified and nurses now spend only an estimated 25% to 35% of their time in the direct care of patients. This increased demand on a nurse's time leads to the perception that there are not enough nurses, although numerically we have more nurses than ever before. The article calls for higher pay to nurses as an incentive for hospitals to seek lower-priced alternatives for accomplishing the non-patient care duties being done by nurses. The article also calls for the creation of additional pairs of hands to "help nurses provide patient care." There are also proposals for intricate and massive system changes in hospital organization, information collection, and the creation of something called "nurse-physician joint practice." These proposals are followed by the previously mentioned jaundiced view of the AMA's RCT proposal from the two-dimensional perspective of the author.

With the exception of the acknowledgement of the need of additional pairs of hands to help nurses, all of the suggestions made by Aiken, even if they were approved for start-up tomorrow, would require many years before they could provide any relief for patients who now are not being adequately serviced at the bedside. Organized medicine is sympathetic to many of the identified items on nursing's professional and economic agenda. They do not, however, address the problem of today's patient who is too ill to get out of bed and go to the toilet without assistance, who needs assistance with being fed a meal while it is still warm and appetizing, or who needs to be properly turned at regular intervals to avoid the development of bedsores. They do not help the patient who needs to be transported promptly to and from a radiology department so that an important diagnostic procedure can be done or a host of similar activities that the RCT proposal would address within a year after start-up. This proposal would offer a practical way to provide needed services in the near term, while any needed system adjustments are being developed and financed to the point that they can be put into place. Many hospitals across the country now have beds—and in some instances whole units—that are not available for patient use because of the shortage of bedside care.

The RCT proposal would prepare a person, through 18 months of staged training, to qualify to care for patients, eventually even in critical care units. This would begin to address the fact that important aspects of nursing capability have been changed over the years since 1966 by the leadership of organized nursing. They seek to put in place a two-entry-level system,[2] each of which would depend solely on collegiate programs. Presumably, these are felt to be more prestigious (hence, more "professional") than hospital-based diploma programs. In the view of organized nursing, there ultimately should be only two-year associate degree programs, yielding an associate degree in nursing from community colleges, and four-year bachelor of science degree programs, yielding a bachelor of science degree in nursing. The former would produce a so-called technical nurse; the latter would provide the so-called professional nurse. In the implementation of this two-entry-level system, the one-year licensed practical nurse program and the three-year hospital-based diploma programs will be replaced.[3] The effectiveness of this plan can easily be grasped when one realizes that in 1960 there were 900 hospital-based diploma programs, and by 1987 this had been reduced to 190 programs. Those are the programs, however, that traditionally prepared bedside nurses. Many physicians are not aware of the fact that, by

contrast, neither the associate degree programs nor the bachelor of science programs require candidates to have operating room or emergency room experience to graduate as a registered nurse. Consequently, surgical technologists now practice in operating rooms, and emergency medical technicians deliver direct care to patients. In fact, it is thought that more than 50% of bachelor of science programs do not require even observational experience in critical care or dialysis units. Somehow, we must provide persons who are properly trained and who can carry out the tasks that are needed by patients. The issues surrounding the professional, political, and economic aspirations of nursing are clearly important and, where appropriate, merit support, but they should not be advanced at the cost of patient needs.

Organized medicine supports unequivocally the recruiting and retaining of nurses at the bedside, but we also believe it is important to recognize that there are many formidable barriers to accomplishing those goals—not the least of which is that competition for college students is increasing. Women who many years ago would have become nurses are now becoming physicians. The size of the female applicant pool for medical school almost quadrupled in the past 35 years, and today there are approximately 20,000 women medical students in the United States. Many of them are women who, 35 years ago, would have been a part of the applicant pool for nursing school. Among college freshmen in a 1986 survey,[4] more women expressed an intent to become a physician than to become a nurse. These are realities we must acknowledge.

Hospitals in my community, like many others around the nation, are currently attempting to recruit nurses from the Philippines, Canada, and Europe. The American Medical Association's RCT proposal offers a mechanism to tap another resource pool inside America that lies outside the loop of current recruitment efforts, which are largely directed to those who have the economic support to go to college for either two years or four years to become either a technical or a professional nurse. The RCT proposal would allow persons to earn while they learn and would thereby offer an opportunity of entering the health care field to many who currently see it as beyond their reach. It clearly offers an opportunity that realistically does not now exist to men, the poor, and to minorities. As they learn, they will be able to advance. They may well aspire to move higher up the health care ladder, perhaps one day returning to school and even becoming physicians. Nothing would please the AMA more. In the meantime, we would be providing something that is seriously needed at this time by the American public.

The registered care technologist proposal is not offered as a total solution, only an alternative worthy of dispassionate, reasoned consideration. Is such an approach feasible? Anyone in the least familiar with how well the hospital corpsmen have performed for many decades in the United States Navy would think a feasibility project should be supported—to find out if, in a civilian setting, a registered care technologist can successfully "help nurses provide patient care" and yet not take the place of a nurse.

We are all, patients and health care professionals alike, in the same time frame of 1989 and must understand as best we can all of the forces that create this environment. Only then can we make intelligent decisions as we "change with the times." We must keep in mind, however, that the obligation of both professions, nursing and medicine, is to serve the needs of patients. The true shortage is of bedside care. We must focus on that, and I sincerely hope our nurse colleagues will reconsider and decide collaboration on this agenda item is in everyone's best interest.

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Additional Thoughts on the Hospital Nursing Shortage

It is worth noting that while the supply of registered nurses has never been higher, the enrollment figures in schools that prepare students for careers as registered nurses have continued to diminish, pointing to a time in the not-far-distant future when the paradoxical aspect will disappear.

Aiken elsewhere in this issue describes a number of situations and concerns with which, in this era, there should be no argument. It is surprising to read that there are directors of nursing throughout the country whose positions are not established as senior members of hospital management and who do not have direct access to the chief executive officer of the hospital. Such failures reflect archaic and unacceptable management practice in this era.

The voting status for nursing directors as members of hospital boards may be more symbolic than real, since it is the rare board that operates other than on an overwhelming consensus on important issues. What is an issue is the attendance, on an official basis, of directors of nursing at board meetings and their opportunity to be heard and understood. The chief executive officer, if he or she is to truly represent the hospital and to act as the agent of the hospital board of directors, must be able to represent nursing and its perspective in a balanced way within the institution and to the board.

Aiken writes about the undesirability of hospitals retaining all registered nurse (RN) staffing as opposed to those institutions that introduce licensed vocational nurses and nursing assistants in their care plans. Currently, most hospitals aim for 60% to 70% RN staffing in their nursing staffs and in their delivery of care patterns if they can attain, through successful recruitment, such levels. It is clear that acute care hospitals have had, by any standards, an increase in the level of severity of illness for those patients who are now admitted to their facilities. The percentage of patients now shifted to outpatient care and outpatient surgery has increased substantially. Those patients who are admitted to the institution, with the possible exception of those needing normal obstetrical care, represent the more severely ill end of the spectrum of illness. It is, in fact, more economical of time, safer for patients, and closer to the reality of the requirement of carrying out patient care regimens that most patient care be provided by a registered nurse. Tertiary care institutions cannot aim their staffing patterns below the 70% RN level.

Comment is made on the unilateral introduction of the

registered care technologist concept by the American Medical Association, one that both hospitals and professional nursing organizations have attacked. This represents a failure on the part of organized medicine and organized nursing to mutually develop solutions to mutual problems.

Health care delivery systems are dependent on nurses who provide hospital care. Opportunities other than nursing have become attractive to many women. Nursing salaries need improvement; however, in an era of increasing cost constraints and reimbursement problems, an impasse is in the making, if not already in place. This issue will be resolved as part of a national approach to health care delivery. What Aiken does not touch upon is the failure within nursing education itself, however. A multitude of RN education programs—baccalaureate, diploma school, associate two-year programs—presents a confused educational approach, particularly in contrast with other professions such as medicine, dentistry, law, and engineering. The nursing profession has not looked to the substantial percentage of the population that does not attend college and particularly those minority groups for whom a career in nursing would represent a notable step towards assimilation into the American culture. Perhaps those remain the major challenges for the health care field, and nursing within it, to resolve.

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Case Reports

Transdermal Clonidine Therapy and Nicotine Withdrawal

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CIGARETTE SMOKING is a problem of major medical[1] and economic[2] proportions. Addiction to nicotine is extremely difficult to combat, with many treatment methods attempted and variable success rates.[3-5] Clonidine has recently been shown to reduce nicotine withdrawal symptoms in the early stages of treatment.[6-9] We report the cases of two smokers treated with transdermal clonidine, both of whom are nicotine-free at 12 weeks of therapy.

Report of Cases

Case 1

The patient, a 71-year-old woman, presented to the University of Arizona (Tucson) Smoking Cessation Clinic with a history of emphysema and 53 years of cigarette smoking, with an average consumption of 20 cigarettes per day. She had tried to quit smoking on numerous occasions including no less than four organized programs, two of which involved the use of nicotine chewing gum. Despite these attempts, she had never quit smoking for more than 24 hours. Problems encountered while trying to quit included nervousness, irritability, and an intense craving to smoke. She scored a 7 on the Fagerstrom nicotine tolerance scale, which correlates with a high dependence on nicotine.[10] Her current medications included prednisone, a metaproterenol inhaler, and oxtriphylline. Her blood pressure was 100/70 mm of mercury, her pulse was 72, she weighed 48.2 kg (106 lb) and was 162.6 cm (5 ft 4 in) tall. On examination of her lungs she had decreased breath sounds with an increased expiratory phase.

This patient was placed on a regimen of a transdermal clonidine patch, which delivers 0.1 mg of clonidine per day for seven days. She was instructed to taper off her smoking over the next four days. She was seen again on the seventh day and had stopped smoking two days previously. Her blood pressure was 90/58 mm of mercury, and she reported being nervous and irritable but felt more comfortable than during any previous attempt to quit, with much less craving to smoke. The clonidine patch was replaced weekly for a total of four weeks during which time she did not smoke. During these weekly visits, she was given instructions on stress management and behavior modification. The clonidine therapy was stopped after four weeks. At five weeks she was again smoking cigarettes, as many as five per day. She was then placed on a regimen of 0.2 mg of transdermally delivered clonidine, and she stopped smoking within 24 hours. Her blood pressure was 90/60 mm of mercury at this time. At 12 weeks from her initial presentation, she is not smoking cigarettes but continues to use transdermally delivered clonidine.

Case 2

The patient, a 41-year-old woman, had smoked cigarettes for more than 20 years but quit a year ago with the aid of nicotine chewing gum. She chews about 20 pieces of gum per day and has tried unsuccessfully on a number of occasions to cut down but has problems with nervousness, irritability, and a failure to concentrate. She had rheumatic fever as a child but has no other significant medical history. On examination her blood pressure was 148/92 mm of mercury, her pulse was 66, she weighed 52.3 kg (115 lb), and was 165.1 cm (5 ft 5 in) tall.

This patient was placed on a regimen of 0.2 mg of transdermally delivered clonidine and was instructed to taper off of nicotine chewing gum over a two-week period. Her blood pressure dropped to 110/72 mm of mercury during this period, and she had mild drowsiness and a dry mouth; she was successful in stopping the gum, however. The clonidine therapy was maintained for an additional two weeks, at which time it was stopped. She has been nicotine-free for 12 weeks at the time of this report.

Discussion

Case 1 is a patient who is heavily addicted to nicotine through cigarettes and for whom treatment in several approaches has failed. The use of clonidine apparently provided some relief of the nicotine withdrawal symptoms that undermined her previous efforts. At 12 weeks of therapy, she is a good candidate for placebo patch therapy. The second patient is a successful graduate of a nicotine gum program who was not able to taper off the gum. Again, using clonidine appears to have suppressed the withdrawal symptoms sufficiently to allow a nicotine taper.

Smoking cigarettes is a complex psychosocial behavior[4] that has multiple influences. One such influence is the addiction to the drug nicotine.[3,11] Glassman and colleagues have shown that the centrally acting α-agonist clonidine can be useful in the treatment of nicotine withdrawal.[6,12] Clonidine in a transdermally delivered form (Catapres-TTS) has also been shown to reduce nicotine withdrawal symptoms of craving, irritability, anxiety, and restlessness when compared with a placebo patch.[7] The simplicity of the transdermal patch makes it especially useful in an office practice.[13] The patch comes in three different doses and provides a steady release of clonidine over a seven-day period.[14] This type of delivery offers the advantages of steady-state blood levels and increased compliance.[15] The side effects of clonidine use are generally mild and include a dry mouth, drowsiness, and a local skin reaction at the site of the patch.[14-16]

Clonidine is a useful adjunct in the treatment of nicotine addiction, especially in a smoking cessation plan that uses behavior therapy in patients who are motivated and persistent in their attempts at abstinence.[17]

(Green JJ, Cordes DH: Transdermal clonidine therapy and nicotine withdrawal. West J Med 1989 Jul; 151:79-80)

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Prolactinoma in a Middle-Aged Man With an Osteoporotic Fracture

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OSTEOPOROSIS OCCURS IN MEN only a sixth as often as in women.[1] Various factors contribute to this sex discrepancy, including the longer life expectancy of women, an increased peak bone mass in men as compared with women,[2] and the absence in men of a distinct time comparable to menopause when levels of circulating sex steroids decline rapidly and loss of bone is accelerated.[3] For both sexes, many factors have been implicated in the etiology of osteoporosis. A decreased intake or absorption of calcium and vitamin D, immobilization, the use of anticonvulsant medications, ethanol ingestion, tobacco use, and various hormonal deficiency and excess syndromes all can cause or contribute to a loss of balance between bone formation and dissolution.[1,4] Except in the extremely elderly, when osteoporosis is found in men, all these factors must be considered before assuming a diagnosis of idiopathic disease. Such an approach to a middle-aged man who was seen because of back pain and evidence of spinal osteoporosis led to the finding of a prolactin-secreting macroadenoma of the pituitary that had caused secondary hypogonadism.

(Taylor SD, Kelly TM: Prolactinoma in a middle-aged man with an osteoporotic fracture. West J Med 1989 Jul; 151:80-82)

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone

Report of a Case

The patient, a 49-year-old man, was referred to our center for a workup for osteoporosis. The diagnosis had been made when he was seen for back pain incurred while swinging a baseball bat. On the initial evaluation he had had tenderness and a decreased range of motion of the thoracic spine without any previous history of skeletal difficulties. Plain spine films had revealed a T-4 compression fracture with anterior wedging as well as general deossification of the thoracic vertebrae (Figure 1). On quantitative computed tomography (CT), the mean spinal bone density was 54.9 mg per cm^3 compared with an age-adjusted normal value of 145.5 mg per cm^3.

The patient's history included a lifelong, large dietary intake of milk products and no use of alcohol or tobacco. He said he had not had previous surgical procedures and did not have gastrointestinal disorders, a change in stool habits, weight loss, or other systemic symptoms. He admitted to ceasing all sexual activity in his marriage some 10 years earlier by mutual consent with his wife, but he did note occasional nocturnal penile tumescence and had fathered three children some 15 years earlier. He was taking a daily calcium supplement that he had personally begun a year earlier as part of a general health maintenance program.

On physical examination he had normal trunk and ex-

Figure 1.—A portion of a thoracic spine film shows a compression fracture, anterior vertebral wedging, and generalized demineralization of the vertebrae.

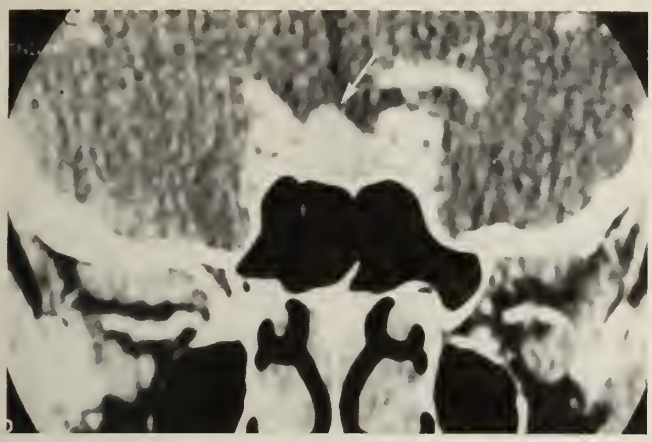

Figure 2.—A computed tomographic scan of the sella turcica shows a pituitary mass with suprasellar extension (arrow).

tremity proportions, normal quality and distribution of facial and body hair, and no palpable gynecomastia. Visual fields were grossly full. The testes measured 3.0 cm in length, and on palpation the prostate was of normal size. The skin was without unusual pigmentation or creases. A back examination revealed only mild, midthoracic tenderness to percussion.

Serum electrolyte levels and renal function were normal as were calcium, phosphate, and albumin levels. The serum testosterone concentration was decreased at 5.2 nmol per liter (1.5 ng per ml; normal 10.0 to 38.0 nmol per liter), and the prolactin level was elevated to 440 μg per liter (440 ng per ml; normal <15). The serum thyroxine was 103 nmol per liter (8.0 μg per dl; normal 51 to 142), the triiodothyronine resin uptake 0.26 (26%; normal 0.25 to 0.36), the serum calcitonin 41 ng per liter (41 pg per ml; normal, nonfasting level, 0 to 22), and the 1,25-dihydroxyvitamin D_3 (1,25-$[OH]_2$ D_3) 115 pmol per liter (44 pg per ml; normal 40 to 130 pmol per liter). The intravenous administration of gonadotropin-releasing hormone (GnRH) produced a rise in the luteinizing hormone (LH) level from 2.3 to 9.9 IU per liter (2.3 to 9.9 mIU per ml) in two hours and a concomitant rise in the follicle-stimulating hormone (FSH) value from 2.0 to 4.2 IU per liter (2.0 to 4.2 mIU per ml). Adrenocorticotropin stimulation produced a normal increase in serum cortisol levels from 220 to 710 nmol per liter (7.9 to 25.9 μg per dl) at 60 minutes. A high-resolution CT scan of the pituitary gland revealed a mass with suprasellar extension (Figure 2). A macroadenoma was resected using a transsphenoidal approach. Sections of the tissue examined using immunoperoxidase showed diffuse staining of cells with antibody directed against prolactin.

After the operation the serum prolactin level remained elevated at 86 μg per liter, so treatment with bromocriptine mesylate was initiated. On a bromocriptine dose of 7.5 mg per day, the patient's prolactin level was less than 5 μg per liter, but a simultaneous testosterone measurement showed a value of only 1.4 nmol per liter (0.4 ng per ml). The patient could not tolerate bromocriptine, however, and the drug was discontinued. Off medication, prolactin levels were 20.8 and 22.4 μg per liter. At the time of the latter measurement, the testosterone level was 4.2 nmol per liter (1.2 ng per ml) and another GnRH stimulation test showed only small increases in LH (from 2.6 to 3.7 IU per liter) and FSH (from 1.3 to 1.9 IU per liter). A regimen of monthly injections of testosterone enanthate was begun. Five months after the surgical resection, with the prolactin level just above the upper limit of normal, the patient's bone mineral concentration by CT was 57.5 mg per cm^3, essentially unchanged from its preoperative value.

Discussion

Women with elevated prolactin levels are often diagnosed early when they have galactorrhea, amenorrhea, or infertility.[5] In contrast, hyperprolactinemia and its associated endocrine abnormalities are difficult to detect clinically in men before a substantial progression of the disorder. The only symptoms present in most male patients with prolactin-secreting pituitary tumors are decreased libido and impotence,[6] symptoms that men usually do not mention spontaneously to a physician and that physicians usually do not inquire about. Although hyperprolactinemia is known to produce osteopenia in men,[7] to our knowledge this is only the second report of a prolactinoma causing overt osteoporosis in a man.[8]

Hyperprolactinemia appears to cause osteoporosis chiefly by producing testosterone deficiency. Increased prolactin levels act on the hypothalamus to disrupt the normal, pulsatile secretion of GnRH, leading to a loss of the usual LH secretory episodes and, as a result, to secondary hypogonadism.[9] A central effect of hyperprolactinemia has been confirmed in studies in animals in which testosterone levels were lowered by castration or by administering prolactin. In such animals, prolactin blocked the expected rise in LH and FSH levels.[10] Prolactin also acts at the gonadal level, at least in male rabbits, inhibiting testosterone secretion in response to both endogenous LH and exogenous human chorionic gonadotropin.[10] Our patient preoperatively, presumably as a result of his hyperprolactinemia, had basal gonadotropin levels that were inappropriately normal in a person with a considerably reduced testosterone concentration. An operative injury to the pituitary gonadotrophs probably contributed to his persistent hypogonadism after the surgical procedure because his testosterone level did not rise even when his serum prolactin concentration returned to normal with bromocriptine treatment and because postoperatively his gonadotropin levels were only minimally responsive to GnRH stimulation.

Besides acting through hypogonadism, increased prolactin levels may act directly to decrease bone mineral content. Schlechte and co-workers reported that amenorrheic women with hyperprolactinemia had reduced bone density whereas amenorrheic women with similar estradiol concentrations but normal prolactin levels did not.[11] An effect of prolactin independent of low sex steroid levels was thus inferred.

Several mechanisms have been proposed to account for the development of osteoporosis in hypogonadal men. First, testosterone may have a direct action on bone because bone contains 5α-reductase, the enzyme found in androgen target tissues, which metabolizes testosterone to its intracellular mediator, dihydrotestosterone.[12] Second, decreased serum testosterone levels may result in a decreased peripheral formation of estradiol, which in turn would favor an increased bone loss. This formulation, however, cannot explain bone loss in normal elderly men who maintain their estradiol and estrone levels despite a fall in the concentration of free testosterone with age.[13] Another mechanism whereby hypogonadism might result in osteoporosis is based on the fact that low levels of testosterone are associated with reduced levels

of calcitonin, a hormonal inhibitor of osteoclastic bone resorption. Testosterone treatment is reported to return calcitonin levels to normal.[14] The patient we describe, however, did not have a low calcitonin level at the time of presentation. Finally, Francis and colleagues have reported that in a group of 13 hypogonadal men, plasma 1,25-$(OH)_2$ D_3 concentrations were substantially reduced in the 7 who had vertebral crush fractures.[15] The low 1,25-$(OH)_2$ D_3 levels, not found by other investigators who also studied hypogonadal men,[16] were associated with the malabsorption of calcium. Subsequent treatment with testosterone resulted in increases both in 1,25-$(OH)_2$ D_3 levels and in calcium absorption. A low level of 1,25-$(OH)_2$ D_3 was not found in our patient.

Although the precise mechanisms for osteoporosis in hyperprolactinemic hypogonadal states remain uncertain, it is known that normalizing the altered hormone levels can reverse the bone loss. Greenspan and associates, who followed up six men treated for pituitary tumors with surgical or bromocriptine therapy, found that after altered levels of prolactin or testosterone were corrected, forearm bone density increased considerably.[7] Testosterone replacement therapy has also been shown to improve a number of histomorphometric values in osteoporotic hypogonadal men, including the indices of bone remodeling.[16,17]

In the evaluation of a case of decreased bone mass in a man, a focused history and physical examination are required, including eliciting a detailed sexual history and an examination of genitalia and of secondary sex characteristics. In addition, testosterone and LH levels should be measured in all osteoporotic men. Obtaining such information early in the evaluation may lead to the diagnosis and treatment of a precipitating factor before the bone loss or its cause produces more serious consequences for the patient.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Low Back Pain Care

To THE EDITOR: It was with interest that I read the recent journal article[1] that attempted to explain the different responses patients had to allopathic and chiropractic care for their back pain. The implication was that chiropractors seem to provide better care.

I agree, having spent 19 years practicing emergency medicine and three years in an HMO orthopedic clinic, that there is no reason not to explain possible mechanisms of injury, advise conservative care, exercise programs, and proper body mechanics to virtually all back pain patients. There are many good printed pamphlets and diagrams available to distribute to patients. Also, a visit to the physical therapist can reinforce the value of initial rest, progressive exercise, and preventive measures.

This study, however, does not address fully the fact that the patients were self-selected. I propose that the distribution of patients is not random and may already create a bias regarding satisfaction and results. The study also does not indicate the number of patient visits and the amount of time spent with these patients.

Many patients seek secondary gains, one of which may be narcotic and sedative medications. Those patients would not choose to go to a chiropractor. Many patients understand that their condition may warrant surgical intervention; they, too, would not seek chiropractic care. Many patients, after personal injuries (such as auto accidents), are referred by attorneys specifically to a chiropractor with whom the attorney has a relationship. These patients will have a very high expectation of success and may even have some monetary gain in the offing.

I am not denigrating the value of chiropractic care because, undeniably, many patients are benefitted by chiropractic intercession, but an unfair comparison is being attempted. Only a prospective study of specifically directed patients to one or the other modality without regard to any other factors would be a valid comparison.

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REFERENCE

1. Cherkin DC, MacCornack FA: Patient evaluations of low back pain care from family physicians and chiropractors. West J Med 1989; 150:351-355

* * *

To THE EDITOR: I am a student at the College of Osteopathic Medicine of the Pacific. Consequently, I read the Cherkin and MacCornack article[1] with great anticipation. I was disappointed, however, by the implication that all allopathic and osteopathic care for low back pain is the same. In fact, many osteopaths incorporate manipulation into their treatments. Thus, in actuality, there are three categories for comparison: allopaths and nonmanipulating osteopaths who use medications and surgery alone, chiropractors who use manipulation alone, and osteopaths who use all three treatment modalities.

The article raised three questions in my mind:

- How many of the family physicians were osteopaths? Allopaths?
- Of the osteopaths, how many used manipulation in their treatment plan?
- What would the percentage of patient satisfaction be if all three treatment modalities were available from the caregiver rather than just one or two?

Osteopaths who use manipulation in their treatment of low back pain approach the problem very differently than their fellow family physicians because they deal directly with the structural lesion and not merely with pain suppression. Thus, they are able to provide the patient with a more thorough treatment because of the increased number of treatment modalities available to them and the knowledge of how to integrate them cohesively.

It would be of interest to see a comparison of patient evaluations of low back pain care between allopathic and osteopathic physicians and chiropractors, for greater completeness and new conclusions regarding this topic.

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1. Cherkin DC, MacCornack FA: Patient evaluations of low back pain care from family physicians and chiropractors. West J Med 1989; 150:351-355

* * *

Dr Cherkin Responds

To THE EDITOR: Thank you for the opportunity to respond to the letters of Saland and Bowers concerning our article on patient evaluations of low back pain care from family physicians and chiropractors.[1]

I agree with Dr Saland that patient self-selection bias might be an explanation for greater patient satisfaction with chiropractors, and we explicitly acknowledge this in our discussion. I think, however, that Dr Saland may overestimate the importance of "secondary gain" in the primary care setting. Our survey of 476 family physicians in Washington determined that the average physician believed that only 13% of visits for low back pain were by patients who were primarily motivated by "secondary gain." Hence, from the family physician's perspective at least, secondary gain is not as important an issue as some may believe.

I also question Dr Saland's assertion that "many patients understand that their condition may warrant surgery" and therefore "would not seek chiropractic care." Since the indications for surgery are often equivocal and nonemergent, one could reasonably argue that patients with these indications might try less invasive forms of therapy—such as chiropractic manipulation—before subjecting themselves to sur-

gery. In fact, chiropractors often characterize their approach as an alternative to surgery.

Ms Bowers is correct in pointing out that osteopaths are a major provider of both manipulative and nonmanipulative care for low back pain. Since only 2 of Group Health's 181 family physicians were osteopaths (both of whom use manipulation), however, it was not possible to separately evaluate osteopathic care. While Ms Bowers' assertion that osteopaths "deal directly with the structural lesion" remains to be proved, I agree with her implication that providers with more tools at their disposal may be better able to meet the needs of their patients. Future research will need to determine which tools make the providers of care for low back pain effective.

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1. Cherkin DC, MacCornack FA: Patient evaluations of low back pain care from family physicians and chiropractors. West J Med 1989; 150:351-355

Unpredictable Adverse Reactions

To the Editor: The Specialty Conference on pertussis in the March issue[1] is provocative. As one who is still experiencing prolonged effects, I can attest to the seriousness of the disease in adults. Given incidence rates for postimmunization reactions of 1 in 140,000 and 1 in 11,000 for serious morbidity and mortality, respectively,[2] risk versus benefit favors immunization. If we also consider disease incidence, acute distress, and protracted convalescence—it is not the common cold—the choice seems to favor immunization even more.

The media can rightfully be blamed for reporting bias and sensationalism, but the medical profession could be more aggressive in its efforts to set the record straight. The principal cause for medical reluctance with respect to pertussis immunizations, however, must be attributed to our legal system. It is here we must look for reform.

When an unfavorable reaction is experienced to a procedure intended to reduce susceptibility to a known serious disease, an awful lot of second guessing takes place. The injured party feels betrayed. The fact that unpredictable adverse reactions are known to occur, that they need not be because of errors or negligence, that state-of-the-art technology is unable to predict host susceptibility to adverse response, and that the physician was duly professional do not seem to be factors in liability. Our legal system encourages the filing of claims against all reachable parties including raw material suppliers, product manufacturers, wholesalers, retailers, clinics, hospitals, physicians, and staff. Regardless of culpability, each defendant incurs expense.

The legal profession agitates for freedom to pursue full recompense for victims under the theory that injury would or should not occur without some type of preventable defect or implied warranty. Society is sympathetic to persons who suffer an adverse reaction, especially when literally thousands of people undergo the same procedure without complication.

Biologic uncertainty and unpredictability need proper recognition. Adverse reactions from immunizations are unpredictable and involve unforeseeable host factors. It seems reasonable to suggest that, as part of the procedure fee, an amount based on adverse response rates be included to compensate victims for expenses in a no-fault scenario. The public seems to demand such insurance, and if such incidents could be removed from contingency litigation, costs could be reduced, not to mention expediency of settlement.

Lawyers cry foul at any suggestion that the need for their services be curtailed. They argue that without legal inquiry, victims might not collect all the law allows—what they are "entitled to." They also argue that legal inquiry is necessary to uncover possible wrongdoing. What is being suggested here is not protection against liability for wrongdoing, but rather that wrongdoing is not necessarily involved in unpredictable reactions. If the public wants to take advantage of preventive medical science, it must be willing to accept the known uncertainties (risks). To demand flawless biologic response when host factors are not controllable is unrealistic.

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1. Cherry JD, Baraff LJ, Hewlett E: The past, present, and future of pertussis: The role of adults in epidemiology and future control (Specialty Conference). West J Med 1989; 150:319-328

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Recognizing and Treating Alcoholism

To the Editor: The article, "Factors Associated With Physician Recognition and Treatment of Alcoholism," by Linn and Yager in the April issue,[1] although covering quite a bit, overlooked several factors.

Many physicians come from homes where one or both parents were alcoholic. Medicine is a natural profession for adult children of alcoholics (ACOAs). Part of the disease of alcoholism, and the ACOA syndrome, is denial that a problem exists. Physicians coming from such homes, who have not been in treatment, will have great difficulty dealing with alcoholism. If they confront someone with alcoholism, often it means they must deal with their own family's problem—something they have been reared not to do.

In their training process, many medical students, interns, and residents deal with populations with a high incidence of alcoholism. The emphasis is often on treating the presenting medical problem, and the alcoholism is often a complicating factor that only gets in the way. We learn to look at alcoholism as something that is an annoyance and not a disease in itself. These populations are also often indigent, and the association of alcoholism with this "undesirable" social class is strengthened.

I think that these factors are as important as the ones mentioned in the article but much less known.

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REFERENCE

1. Linn LS, Yager J: Factors associated with physician recognition and treatment of alcoholism. West J Med 1989; 150:468-472

A New Role for American Medicine?

To the Editor: I want to thank you for your editorial comments in the March[1] and April[2] issues of the journal.

Each of these editorials shows your admirable vision beyond the narrow parochial viewpoint often expressed in medical periodicals, and, for me, point to a new, broader role for American medicine in redefining not only the health but also the security of the nation and the planet.

As you point out, the health of a nation means more than the absence of illness. It is determined by many other factors, among them the health of our physical environment, the soundness of our economic system, our educational system, our health care system, our social welfare and political systems, in an increasingly interdependent world.

Likewise, the security of a nation means more than the number of exotic weapons we can and do build or the size of our military budget—perhaps the latter is in inverse relation to our real national health. National security means, rather, the vigor with which we protect our environment, educate our young, care for our elderly and disadvantaged, and build our economy, which in the long run will provide sustained, imaginative, and rewarding employment, taking full advantage of the brain power now being consumed in a senseless arms race.

As you note, the urgent need to address these problems has been recognized by the environmental movement. I would point out that many other groupings within the broader peace movement have likewise been involved in efforts towards these new goals.

The national meeting of Physicians for Social Responsibility in March in Palo Alto, California, had as its focus redefining national security and addressed just these issues.

The San Francisco Bay Area chapter of Physicians for Social Responsibility is planning a major conference in San Francisco on October 7, titled "Building Global Security."

I suggest that the "potent third force" that you feel is needed for leadership in this movement need not "be created." It exists. What better role could be tailored for organized medicine?

I urge that county, state, and national medical associations seriously discuss leadership roles for themselves and that they promptly involve themselves in the planning and funding of such conferences.

The problems of the environment alone are too large for any one nation to hope to solve. The obvious international (global) cooperation required could convert perceived adversaries into allies, and, I hope, reduce the need, perceived by some, for a continuing arms race. Perhaps then we can have sufficient funds so that we no longer need to think about rationing health care.

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REFERENCES

1. Watts MSM: A critical moment in our history (Editorial). West J Med 1989; 150:341-342
2. Watts MSM: A nation's health in jeopardy (Editorial). West J Med 1989; 150:456

Myositis Due to *Salmonella enteritidis* Bacteremia

To THE EDITOR: Myalgia and myositis have been observed in various viral and bacterial infections, including influenza A,[1] leptospirosis,[2] and legionnaires' disease.[3] Although myalgia and elevation of muscle enzymes have been noted in cases of typhoid fever,[4] nontyphoid salmonellosis has previously not been reported as a cause. We describe a case of *Salmonella enteritidis* bacteremia associated with myositis.

Report of a Case

A 79-year-old man was admitted to San Jose (California) Hospital in January 1989 with a two-week history of progressive weakness, myalgia, and constipation. He also noted fever and chills. His weakness progressed to the point where he had difficulty standing. He had a history of hypertension. He had not fallen and did not drink alcohol.

On examination, his blood pressure was 102/52 mm of mercury, his heart rate was 100 per minute, respirations were 16, and his temperature was 38.5°C (101.3°F). He was found to have generalized muscle weakness. His cardiopulmonary, abdominal, and neurologic examination results were otherwise normal. The leukocyte count was 13.1×10^9 per liter (13,100 per μl), with 0.93 neutrophils, 0.02 band forms, 0.03 lymphocytes, and 0.02 monocytes. The creatine kinase level was 1,363 units per liter, aldolase 22.7 units per liter, and aspartate aminotransferase 127 units per liter. His stool and four blood cultures grew *S enteritidis.* The patient was treated successfully with antibiotics. The results of a urinalysis one day after antibiotic therapy were normal. His muscle weakness resolved, and the muscle enzyme values returned to normal.

Salmonella species bacteremia is characterized by a febrile course, often accompanied by gastrointestinal symptoms, splenomegaly, and rash. Our case is unique in that myositis was one of the presenting symptoms of *S enteritidis* bacteremia. Proposed mechanisms for muscle involvement in bacterial infections include direct muscle invasion[2] and the production of a circulating proteolytic toxin.[5] *Salmonella* species bacteremia should be considered in the differential diagnosis of patients with fever and myositis, particularly in patients such as the elderly or the immunocompromised, who are at risk for serious or life-threatening salmonellosis.

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Rational Rationing

To THE EDITOR: The article by Crawshaw and colleagues[1] and the accompanying editorial[2] in the March issue call attention to the growing involvement by the public in the awesome choices that must be made as a result of the increasing demand for and the constraints of limited resources. The necessary outcome of this squeeze is that health care is rationed. This is probably not a revelation to most providers and payers, but having this rationing be overt and explicit makes most people quite uncomfortable. Whereas most people in the health care delivery system readily acknowledge that everyone can't have everything he or she needs, no one wants to be the person with the sad task of telling Coby Howard's mother that he was "not entitled" to a transplant.

The public is becoming increasingly sophisticated about health care, and it is now a major political issue at local, state, and national levels. Providers, payers, and politicians are

well advised that rationing decisions are, as the articles indicate, decisions that must reflect more than simply the values of those groups. Informing and involving the community in this process is therefore not only desirable but necessary.

Oregon, the first state to formally engage the public in addressing these issues, has now been joined by several others across the country. In the largest state, California Health Decisions, a private, nonprofit educational organization, has been in existence for over four years. Although most of our activities have taken place in Orange County, we also have chapters in Sacramento and Los Angeles. Local public interest and press coverage have been remarkable, and numerous state and local officials, legislators, and professional and business organizations have responded to invitations to be part of the process of educating citizens and hearing their views. In Orange County, California Health Decisions was instrumental in conveying community concern for prenatal care to the Board of Supervisors, resulting in their allocating 500 additional slots for such care. This reflects an apparently commonly held view that preventive care should take precedence over attempts to cure. While this may not be surprising, having it stated so clearly seems to be an indispensable benefit for those who are now providing and allocating health care resources, and this process deserves widespread support.

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HRT DOC

To THE EDITOR: It is the age of the politics of envy. Self-serving demagogues have seized upon the natural human emotion of jealousy and created a time dominated by special interest groups united by half-truths and fueled by hatred. The paintbrush of their envy is as broad as it is indiscriminate. The successful, the wealthy are the bad guys—the exploiters; the poor, the nonachievers are the good guys—the exploited.

That our profession is a target in this "class warfare" is not without some merit. Charges of greed and corruption are all too often based on fact.

Physicians, as well, are not immune to this call to envy. The spectacle of interspecialty warfare, energized and exploited by government legislation, has seen the viability of our profession sacrificed at the altar of personal agendas.

If we do not begin to effectively police ourselves and become aware of the social milieu in which we work, our profession is doomed, and the patient will be the ultimate loser.

The other day I was passed by a new, large Mercedes with a license plate reading HRT DOC. No more need be said.

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Seminars in Health Care Delivery

The Hospital Nursing Shortage

A Paradox of Increasing Supply and Increasing Vacancy Rates

LINDA H. AIKEN, PhD, *Philadelphia*

This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

A serious shortage of nurses has developed since 1984 despite a growing number of employed nurses and a substantial decline in the number of hospital inpatient days. The evidence suggests that the shortage is the result of an increased demand for nurses, not a decline in supply. The increased demand in large part has resulted from the substitution of registered nurses for licensed practical nurses, aides, and other patient services personnel. The substitution was feasible because nurses' wages have been depressed compared with those of other hospital employees. The shortage is likely to abate if nurses' wages increase, making substitution more costly. Even in the absence of continuing wage increases, hospitals could ease the shortage by restructuring patient services and enabling nurses to spend a greater portion of their time in direct patient care.

(Aiken LH: The hospital nursing shortage—A paradox of increasing supply and increasing vacancy rates. West J Med 1989 Jul; 151:87-92)

Vacancy rates for nurses in the nation's hospitals have almost tripled since 1984. More than 75% of all hospitals report a shortage of nurses; almost one in five describes their shortage as severe. Nearly a third of hospitals in urban areas (30%) and 15% of rural hospitals reported closing hospital beds in 1987 as a result of the nursing shortage. The US Department of Health and Human Services Secretary's Commission on Nursing concluded recently that the reported shortage of nurses is "real, widespread, and of significant magnitude."[1]

There have been cyclical shortages of nurses since World War II, but the current shortage is particularly perplexing. The supply of nurses in the United States has increased substantially in recent years to about 1 registered nurse for every 135 Americans (most of whom are healthy). Moreover, during the period in which the current shortage developed, the use of hospital inpatient facilities declined notably. There were 50 million fewer inpatient hospital days in 1987 than in 1981. This scenario would suggest a surplus of nurses rather than a shortage. As recently as the fall of 1988, the Department of Health and Human Services, in its report to the President and Congress, concluded that the supply of nurses was in balance with requirements until into the next century.[2]

The Paradox of More Nurses and More Vacancies

There are several commonly held misconceptions about the causes of the nursing shortage. One is that dissatisfied nurses are leaving the profession in large numbers. While job dissatisfaction is common among nurses,[3] approximately 80% are employed, which is a high employment rate for a predominantly female occupation. Only about 5% of registered nurses work in non-health-related jobs, suggesting that the specialized nature of nursing education does not permit nurses to move easily into other occupations of comparable status.

It has also been suggested that the growing number of jobs for nurses in ambulatory care and new jobs in the health industry, including insurance claims review, hospital preadmission screening programs, risk management, quality assurance, and others, have siphoned nurses away from hospital practice. To the contrary, hospitals have increased the number of nurses employed in the aggregate and the ratio of nurses to patients by more than 25% since 1982.

Enrollments in nursing schools have fallen substantially—26% since 1983—causing great alarm as to the future supply of nurses. Despite declining numbers of graduates, however, there are still many more new graduates coming

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ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
ICU = intensive care unit
LPN = licensed practical nurse
RCT = registered care technologist
RN = registered nurse

into the employment pool each year than nurses leaving. Even if the trend in lower enrollments continues, the actual supply of employed nurses is expected to continue to increase until after the turn of the century.[2]

The current nursing shortage, then, has not been caused by a decline in the number of nurses working in hospitals but by an increase in the number of additional nursing positions offered by hospitals.[1] In economic terms, the nursing shortage is demand driven. The increased employment of nurses by more competitively positioned hospitals has resulted in substantial shortages in less competitive hospitals and during unpopular night and weekend hours and leaves fewer nurses available for positions in nursing homes and other settings.

The increased demand for hospital nurses can be explained in part by changing patterns of hospital care. The average length of a hospital stay has fallen by 7% since 1982. Discretionary admissions have been reduced as a result of preadmission screening programs, improvements in noninvasive diagnostic technology, and other changes in medical practice, including the increased use of ambulatory surgical procedures. On the one hand, these changes reduce the demand for nurses because inpatient days are fewer. On the other hand, the nursing care needs of the average patient in hospital are reported to be greater. These two changes should be offsetting in terms of nursing hours required overall.

Another factor affecting the demand for nurses is the doubling of the number of intensive care unit (ICU) beds since 1973 from more than 40,000 to 90,000 today. Hospitals have added more than 17,000 new ICU beds just since 1980. The percentage of intensive care days and neonatal intensive care days relative to the total inpatient days has increased. Some research suggests that ICU beds are often used for patients who do not benefit, either because they are not sick enough or because they are terminally ill.[4] Nevertheless, ICU beds commit hospitals to a higher ratio of nurses to patients because, on average, it takes four nurses to staff each ICU patient around the clock, compared with one nurse for each patient on a general hospital unit.

The above factors partially account for the increased employment of nurses by hospitals since 1982, but they fail to provide a convincing explanation for all of the substantial increase in nurse employment during a period of notable reduction in hospital capacities nationally. In essence, employers are hiring more nurses than can be accounted for solely on the basis of population need. This explains why federal staffing analysts conclude that the supply of nurses is in balance with national requirements in the midst of a perceived nursing shortage.[2] The federal model is based on estimates of national requirements for nurses, not employer demand.

Widespread Substitution of Nurses

A major determinant of the demand for any kind of worker is the cost of hiring that worker compared with possible alternatives. Nurses are versatile in a hospital context.

Figure 1.—The graph shows nurses' salaries as a percentage of other hospital workers' salaries, by year.

They perform a wide range of functions in addition to nursing care and require little supervision. As a consequence, the number of nurses employed is determined, in part, by nurses' wages compared with those of alternative workers or compared with the cost of alternative systems such as computers. When there is a narrow difference between the market wage rates for nurses and those for other kinds of hospital employees, hospitals prefer to hire nurses.

Over the past two decades, nurses have replaced large numbers of licensed practical nurses (LPNs) and aides in hospitals. In 1968 approximately a third of nursing service personnel were nurses; today more than 60% are nurses. Many hospitals have adopted all registered nurse (RN) staffs. One important explanation for this shift toward more nurses was a narrowing of the wage differences between nurses and LPNs and aides.[5] The wages of LPNs, for example, are now about 73% of those of RNs.[6] When costs of supervision and limitations of legal practice are factored in, at current wage rates nurses are a more economical choice for hospitals than LPNs or aides. Under the wage rates that have prevailed over the past two decades, it was cost effective for hospitals to move toward all nurse staffs.[7,8]

The introduction of Medicare's prospective payment system in 1983-1984 appears to have escalated previous trends and resulted in substantial changes in the labor mix in hospitals. Between 1979 and 1982, hospitals employed 3.2 RNs per LPN. Beginning in 1983-1984, the ratio began to climb, reaching 5 RNs per LPN by 1986. Between 1982 and 1987, hospitals reduced LPN employment by more than 67,000 full-time-equivalent positions. Over the same period, the number of RN full-time-equivalent positions per 1,000 adjusted patient-days increased by 18%. Clearly, the introduction of the prospective payment system resulted in a substantial escalation of the trend to substitute RNs for LPNs.

In addition, in the early years of the prospective payment system, hospitals reduced the size of the overall work force, cutting more than 300,000 non-RN and non-LPN full-time-equivalent positions between 1982 and 1985. In contrast, the number of full-time-equivalent nurses increased by 40,000 during the same period and by 137,000 during the longer period of 1980 to 1987. Hence, a picture emerges of a restructuring of the work force in hospitals, with a greater reliance on nurses.

When wage patterns are examined, some of the reasons for the substitution are clear. Figure 1 traces the relationship between nurses' wages and those of other hospital employees since 1980 in a panel of 73 hospitals, medical centers, and medical schools.[6] In 1983, nurses' salaries on average were

12% higher than those of a group of non-nurse hospital workers, including administrative assistants, computer operators, medical technicians, personnel specialists, pharmacists, physical therapists, physician assistants, respiratory therapists, social workers, and unit managers. Following the introduction of Medicare's prospective payment system, nurses' annual wage increases fell behind those of other hospital workers. Despite a national shortage, nurses' salaries increased only 4.3% in 1986 and 3.1% in 1987. By 1987 nurses' salaries were less than 97% of those of other hospital employees. Preliminary data from 1988 indicate that nurses' salaries have begun to rise again. To prevent a widespread substitution of nurses for others, nurses' salaries would probably have to be substantially higher than those of alternative workers because nurses are so versatile in a hospital context and because they are viewed as contributing to good quality care, a matter of considerable value in an increasingly competitive hospital industry.[9]

Cost-containment programs such as Medicare's prospective payment system appear to have more of a dampening effect on nurses' salaries than on those of other hospital employees (Figure 1).[10] Nursing service is often the largest single labor component in hospitals' budgets, which makes nursing an obvious target when budget reductions are required. Health economists have described nursing as a captive labor market.[11,12] Most nurses are tied to local labor markets because of family considerations. There is little demand for nurses outside traditional health care settings. Most of the jobs for nurses in the ambulatory sector remain filled because nurses prefer the more regular hours. Thus most nurses, if they want to work, are left with the options of hospitals or nursing homes. Nursing homes cannot compete with hospitals on a salary basis, and hospitals tend not to compete with one another for staff on this basis except in highly competitive local labor markets with many hospitals.

The artificial depression of nurses' salaries can be seen most clearly in the lifetime earnings potential of different occupational groups. The maximum salary hospital nurses can expect to earn is only 36% higher than starting salaries, about a $7,000 difference in current dollars. This compares to a salary progression of 72% for secretaries, 89% for personnel directors, 110% for purchasing clerks, 193% for accountants, and 226% for attorneys.[13] For nurses, 20 years' experience has been estimated to have a salary premium of about 5 cents an hour.[14] The low relative lifetime earnings potential of nurses is thought to be a factor in declining enrollments in nursing schools and in the erosion in the quality of the applicant pool. Nursing students have lower average Scholastic Aptitude Test scores than university students in other majors, and the gap between nursing students and others on college campuses is increasing. The possibility of an erosion in the nurse applicant pool is a source of concern, given the ever-increasing complexity of medical care.

Those in occupations with wage problems similar to those of nurses, such as teachers, have resorted to aggressive collective bargaining. A minority of nurses belong to unions, and many are reluctant to support strikes because of the possible adverse effects on patients. Recent rule changes proposed by the National Labor Relations Board that permit bargaining units to consist of all RNs may stimulate greater unionization of nurses in the future, however.[15]

We have documented elsewhere that over the past 25 years, there has been an inverse relationship between nurses' relative wages and hospital nurse vacancy rates.[16] The decline in nurses' relative wages over this period can be traced to various cost-containment efforts, from hospital wage and price controls in the Nixon administration to hospitals' voluntary cost-containment efforts of the 1970s, state rate setting, and finally by the prospective payment system in the 1980s. The evidence suggests that nurses' relative wage rates are inversely related to hospital vacancy rates, primarily because low relative nurses' wages lead to the substitution of nurses for others. We are not suggesting that some nurses have entirely different roles in hospitals as a result of substitution. Rather, we contend that every nurse is spending a substantial portion of his or her time in non-nursing activities that could be done by others. Time and motion studies of nurses show that nurses spend only about 25% to 35% of their time in the direct care of patients.[17,18] Most of the remainder is spent in indirect patient care activities, including charting and clerical work, administrative functions, patient transport, and communicating.

Possible Solutions

A recent Gallup poll indicates that only 20% of hospital chief executive officers believe substantial pay increases for nurses would solve the shortage (*Health Week*, August 8, 1988, p 26). In general, hospital administrators do not think that pay increases attract additional nurses into local labor markets, and the evidence suggests that this is correct because 80% of nurses are already working. The point that is often overlooked, however, is that when nurses' wages rise substantially, there are increased incentives to use them more appropriately. For example, there seems to have been a notable increase in nurses' salaries in Boston in 1988, and it is there that the idea of nurse case managers as replacements for primary nursing has been most aggressively promoted. The assumption underlying the concept of case management is that fewer nurses will be needed than in a primary nurse model of staffing.

Increased salaries may also contribute to solving the shortage by encouraging the more than 500,000 nurses who work part-time to increase the number of hours they work. Many of the popular short-term solutions to shortages of nurses on nights and weekends offer full-time pay for part-time work, which encourages nurses to work part-time or to leave hospitals for work through agencies where they can command these same high hourly wages for full-time work. In addition, trends over the past 25 years suggest that higher wages have an effect on enrollments in nursing schools. Each major increase in nurses' relative wages has been accompanied by increased enrollments in nursing schools. Preliminary reports from nursing schools across the country indicate that enrollments increased in 1988 for the first time in five years, particularly in baccalaureate programs. It is too early to tell whether the increase will be a trend and whether it can be linked with recent increases in nurses' wages.

Increasing salaries in response to the current nursing shortage is likely to reduce or eliminate nursing vacancies because hospitals would have a strong economic incentive to provide care using fewer nurses. If this happens naturally, it is likely to happen first in local labor markets where many hospitals compete for a limited pool of nurses.[9] From a public policy perspective, it appears that an unintended consequence of hospital cost containment is the creation of nurse shortages due to a depression of nurses' wages relative to

those of other occupations. Solving that problem, however, is a challenge. A hospital rate increase would be costly and would not necessarily be used to adjust nurses' wages. Also, earmarking funds for nurses runs counter to the underlying rationale of the prospective payment system. If the market fails to make a correction on its own over the next year or two, however, some form of intervention may be in the public interest.

Even in the absence of economic incentives, hospitals should be restructured to enhance their use of nursing resources. There are simply not enough people who want to be nurses to continue to use nurses so indiscriminately. The objective of restructuring is to reduce the number of nurses required without reducing direct nursing-care hours per patient day. This requires building a support system around nurses that enables them to increase the percentage of their time spent in direct patient care. The following changes would help accomplish this.

Administrative Support

It is hard to imagine another industry of the size and complexity of hospitals that has so few support personnel for its professional staff. Many head nurses run the equivalent of multimillion dollar businesses without even a secretary. The addition of a modest complement of secretaries or administrative assistants to nurses could go a long way in freeing nurses to spend their time with patients.

Unit Management

Nurses and physicians cannot take care of patients efficiently unless other departments meet reasonable performance standards. Yet nurses often have little recourse in cases of poor performance of support services but to take time away from nursing care to provide the services themselves. Providing fresh water, transporting patients to tests and therapy, preparing rooms for new admissions, handling food trays, obtaining drugs and supplies, and providing directions and assistance to visitors are all examples of things that need to be done but not by a nurse. At the least, nurses must have more influence over the performance of hospital support services. An improved management structure could be developed to remove these responsibilities from nurses.

The original concept of unit management, as pioneered at the University of Florida in the 1960s, seems applicable to solving this problem. Unit managers were to be professional hospital administrators with the designated authority from central hospital management to control support services at the unit level. Unit managers were to hold a position of authority in the organization comparable to that of the head nurse or clinical nursing director. Physicians would be represented at the unit level by a clinical medical director. This team of three representing nursing, medicine, and administration would jointly make the decisions necessary to maintain an environment conducive to efficient, high-quality patient care.

The concept of unit management as originally envisioned was not widely implemented. There were not enough hospital administrators in the 1960s to recruit them to such positions as unit managers, and nurses were a less expensive substitute. Unit managers have become, for the most part, glorified ward clerks without the power and authority from central administration to get things done. There are now many more people beginning careers in hospital administration who could benefit from experiencing management closer to the basic product of hospitals—patient care. For this concept to work, however, unit managers must be responsible 24 hours a day every day and must function in an organizational context that balances the requirements and priorities of nurses and physicians with those of the support services.

Assistants to Nurses

New strategies are needed for the effective use of nonnurses in activities related to patient care. Aides and LPNs could be used more creatively to help nurses provide care—in essence, to serve as another pair of hands. Patients in hospitals today are too sick to have their care delegated to technical and informally trained staff, but assistants to nurses could enhance nurses' productivity and effectiveness and improve the overall quality of care.

Improved Systems

According to testimony by Ernst and Whinney, Inc, before the US Department of Health and Human Services Secretary's Commission on Nursing in September 1988, hospitals invest only 2.4% of their operating budgets on information technologies compared with 8% for banks and 11% for insurance companies. Much of the existing computer capacity in hospitals is directed toward billing and third-party reimbursement, not clinical care. Nurses spend an estimated 40% of their time on paperwork, and much of the overtime paid to nurses is for charting. A greater investment in clinically based computer systems could lead to a more cost-effective use of personnel in hospitals and also provide a more systematic data base on which to make clinical decisions and conduct research.

Shared Professional Values

The nursing turnover is estimated to range between 11% and 30% annually, at a cost to hospitals of as much as $3 billion.[1] While nursing is an occupation with a relatively high degree of inherent stress due to the psychological demands of caring for sick and dying people, much of the stress perceived by nurses is organizationally induced. Nurses report that they have little control over their work environment and the factors affecting the quality of care provided to patients, yet they hold themselves accountable for their patients' outcomes. They want less central decision making, self-contained clinical units where a cohesive professional staff can be developed without constant reassignments to cover shortages in other parts of the hospital, a greater flexibility in working hours, and greater autonomy in the practice of their profession. Indeed, hospitals that have been successful in recruiting and retaining nurses during times of national shortages have these organizational dimensions.[19]

Several blue-ribbon panels convened to study the nursing shortage over the past decade have directed recommendations concerning these organizational dimensions to hospital chief executive officers and boards.[20,21] With a few notable exceptions, these recommendations have been ignored and the shortage has persisted. Recent evidence suggests that nurses are still largely outside the decision-making structure of hospitals, which probably accounts for the lack of responsiveness of hospitals to proposals for organizational change. At the request of the Department of Health and Human Services Secretary's Commission on Nursing, the Office of the Inspector General recently did a study of nurse participation

in hospital decision making.[22] The study consisted of a telephone survey to chief executive officers and chief nurse officers of a random sample of hospitals selected from the universe of Medicare-certified, acute care nonspecialty hospitals in the United States.

Chief executive officers were the only members of hospital management who consistently attended meetings of their governing bodies. Some 85% of them were members of the governing body, and about 65% voted. In contrast, less than 2% of all nurse executives were voting members of hospital boards, and only a third regularly attended board meetings. Chief executive officers appear to be the major conduit of information on nursing and patient care to their boards. The Inspector General's findings do not reassure us that the chief executive officers of hospitals routinely have access to the best information on nursing. For example, less than 5% of chief nurse officers were members of their hospital's executive committee, and none of those surveyed voted. Of chief nurse officers surveyed, 6% were members of the finance committee. Only half were voting members of joint conference committees, and only a third participated on planning committees. Excluding nurses from policy-making roles in hospitals limits the availability of information on nursing and related patient care issues and reduces the flow of information to nurses about institutional objectives and challenges.

One of the most frequent and persistent criticisms of hospitals is that services are fragmented, inefficient, and impersonal. Public opinion polls suggest that consumers feel increasingly that hospitals put too much emphasis on the financial aspects of their institutions and too little on the reason for their existence—the care of sick people. The more businesslike hospitals have become in the public's mind, the lower the level of trust and confidence the public has in hospital administrators and physicians. As a result, the quality of hospital care in the United States is ranked by the public somewhat better than that of automotive repair shops but worse than that of supermarkets and airlines.[23] The business model adopted by many hospitals needs to be balanced by the patient care perspectives that nurses and physicians bring.

Nurse-Physician Joint Practice

Unsatisfactory relationships with physicians are a major source of dissatisfaction among nurses and a common reason for resignations.[24] Moreover, it is increasingly clear that patient outcomes depend on the nature and quality of communication between nurses and physicians. A recent multihospital study of the effectiveness of intensive care concluded that the differences in mortality rates among hospitals could be attributed in large part to the nature of the communications and decision-making partnerships between nurses and physicians.[4] This finding is not at all surprising when we consider how rapidly the condition of critically ill patients changes and the importance of anticipating and preventing a catastrophic event rather than treating it under emergency conditions.

Nurses and physicians often do not fully appreciate the responsibilities and obligations that each holds for patients. This could be overcome by organizational arrangements for patient care in which specific nurses and physicians have longitudinal responsibility for the same groups of patients, as is the case in intensive care units where the relationships between nurses and physicians are consistently better than on the general medical and surgical units. Nurses often let their responsibilities for "managing" the unit divert them from maintaining the kinds of longitudinal responsibilities that physicians usually have for patients. It would be much more productive for physicians to support and participate in the restructuring of hospitals to reduce the administrative burden on nurses, enabling them to more fully participate in direct patient care than to propose an alternative bedside provider.

The Registered Care Technologist Proposal

Bringing an end to the persistent shortage of nurses requires the active involvement of physicians. The recent proposal developed unilaterally by the American Medical Association (AMA), however, to train a new category of health care worker as a solution to the nursing shortage diverts attention and resources from the pursuit of a permanent solution.

The proposal calls for the education of a new category of "bedside care givers" to execute medical protocols with special emphasis on technical skills.[25] A registered care technologist (RCT) would receive on-the-job training of from 2 to 18 months' duration. Basic RCT training for nine months would qualify the graduate to provide bedside care to patients in hospitals and nursing homes. Advanced RCT training of 18 months would qualify high school graduates to care for patients in all types of critical care units, including administering intravenous drugs. Training RCTs is envisioned as hospital-based, following the model of diploma nurse education and with stipends for those in training. Registered nurses "who wish to remain at the bedside" would be eligible to be certified as advanced RCTs. The AMA anticipates that RCTs would be paid between $15,000 and $18,000 a year and that the new career would appeal to a pool of applicants not currently considering nursing, namely men and those persons requiring an income during their training period.

The major problem of the RCT proposal is that it does not address the root cause of the nursing shortage—the excess demand for nurses. Moreover, there are some 900,000 licensed practical nurses already trained and experienced in hospital care that hospitals have shunned in favor of registered nurses. The expected wage rates of RCTs are even closer to the wage rates of nurses than those of LPNs, a difference of only a few thousand dollars a year at current wage rates.

It is not clear why there would be a demand for RCTs since the demand for LPNs has declined dramatically. The better solution is moderating the demand for nurses by reducing nurses' responsibilities for unit administration. If the time nurses spend in direct patient care were doubled from the current between 25% and 35% to between 50% and 70%, the nursing shortage would be over. It makes much more sense to substitute clerical, administrative, and support personnel for nurses in nonclinical roles than to have less qualified personnel delivering bedside care to critically ill patients.

The AMA proposal is yet another example of the failure of nurses and physicians to develop mutually acceptable solutions to problems that affect the professional practice of both groups. Nurses primarily support and complement medical care. The expanded clinical responsibilities of nurses have freed physicians to perform medical functions that require

their unique expertise and that tend to be more remunerative than most functions that nurses perform. Because nurses' remuneration derives from the hospital budget, whereas physicians' incomes are primarily fee-for-service, gains for nurses are unlikely to affect the economic status of physicians. A continuing shortage of nurses may adversely affect physicians' incomes, though, if the number of hospital admissions and surgical procedures is reduced because of the shortage. Thus, physicians and nurses both have a stake in solving the hospital nursing shortage and, working together, can promote their mutual interests and those of their patients.

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Health Care Delivery

A Peer Review of a Peer Review Organization

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Under Medicare, one of the federally required objectives of peer review organizations is to reduce inappropriate and unnecessary admissions. We reevaluated 32 admissions approved and 32 denied by the Arizona peer review organization, Health Services Advisory Group (HSAG), in a "blind" manner to determine whether practicing physicians in the community agree with the local peer review organization. Overall, physicians at the Scottsdale Memorial Hospital (SMH) approved 72% of HSAG-approved and denied 61% of HSAG-denied admissions. Of the 64 admissions, 3 or 4 of 4 reviewers (2 physicians and 2 nurses) agreed with the HSAG decision in 38 (59%), but 2 or more reviewers disagreed in the other 26 (41%). Disagreement between the 2 physicians occurred in 48% of the cases and disagreement between the 2 nurses in 33%. Even among admissions denied by SMH physician reviewers, the physicians would have admitted 23% of those patients under similar circumstances. In 28% of the HSAG-denied admissions, the reviewing physicians thought that the patients' health care would have been compromised if the admissions had not taken place. Despite well-defined criteria for the appropriateness of hospital admissions, the review process remains subjective, with much disagreement between peer review organizations and practicing physicians.

(Dippe SE, Bell MM, Wells MA, et al: A peer review of a peer review organization. West J Med 1989 Jul; 151:93-96)

Recent changes in the approach to medical care for Medicare patients have placed a greater emphasis on the cost of providing that care. The federal government has contracted with peer review organizations to monitor hospital use and the quality of care for these patients[1,2] and has established objectives and criteria that the local peer review organizations are to follow.[3]

One of the mandates of Medicare is that admissions to hospital must be appropriate. Admission of a Medicare patient can be denied if the patient does not meet both of the following criteria:

- Severity of illness—the patient is sick enough to require admission to hospital,
- Intensity of services—the patient must receive services that require a hospital setting.[4]

This review process is carried out in Arizona by Health Services Advisory Group, Inc (HSAG). We undertook this study to determine if practicing physicians in the community agree with HSAG decisions and to examine physicians' attitudes regarding Medicare admissions.

Methods and Materials

The cases reviewed were all of patients admitted to Scottsdale (Arizona) Memorial Hospital (SMH), a 340-bed acute care community hospital. The first 32 Medicare admissions denied by HSAG beginning May 1, 1986, and ending November 3, 1986, were included in the study. During the same period, the first 32 admissions evaluated by HSAG physicians and approved were also reviewed.

During the study period, 5% of all Medicare admissions were reviewed by an HSAG nurse. If the nurse thought a patient's case did not meet the criteria, the patient's medical record was reviewed by an HSAG physician reviewer. If he or she approved the admission, the decision was final. If denial was recommended, the admitting physician was notified that a denial was pending and was given a chance to explain to HSAG the reason for the admission. If then the admission was denied, a denial letter was sent to the patient, the hospital, and the physician. The physician or the hospital could appeal the denial, and, if successful, the denial would be overturned. A similar review process by a Missouri peer review organization for Medicare admissions was described by Akhter.[5]

A total of 16 Scottsdale family physicians volunteered to participate in the study, and 3 review nurses employed by the hospital acted as nurse reviewers. One nurse had extensive experience reviewing for HSAG before being employed by Scottsdale Memorial Hospital, and the other two nurses were actively engaged in the review process at the hospital.

Each case was reviewed independently four times by two different nurses and two different physicians. They did not know which cases were approved or denied by HSAG. The criteria they used were the same as those used by HSAG.[4]

The medical records were first reviewed by one of the SMH nurses. Then one of the physicians reviewed the records, making a determination of approval or denial and answering 15 questions related to each case. Five questions dealt with the reviewer's familiarity with the case. None of the cases were even remotely familiar to any of the reviewers. The other ten questions dealt with the physician's attitudes about the care rendered and how he or she would

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ABBREVIATIONS USED IN TEXT

HSAG = Health Services Advisory Group, Inc
SMH = Scottsdale Memorial Hospital

have handled the case under similar circumstances. Each physician reviewed a total of eight medical charts during two 1-hour sessions. They were asked not to discuss the cases after these sessions.

Results

The mean age for HSAG-approved cases was 74 years and for denied cases 76 years, with a range of 49 to 95 years. The mean length of stay for both groups was 5 days, ranging from 1 to 18 days. The mean time between discharge and notification of denial was 168 days.

Overall, physicians from Scottsdale Memorial Hospital approved 71 admissions and denied 57, which compares with 64 approved and 64 denied by HSAG (considering each patient twice; Table 1). Of the 64 HSAG-approved cases, 18 (28%) would have been denied by SMH physician reviewers. On the other hand, of the 64 HSAG-denied cases, 25 (39%) would have been approved by SMH physicians.

The SMH nurse reviewers were asked if they would have referred the case to a physician reviewer. Of the HSAG-approved admissions, 15 (23%) would not have been forwarded to the physician reviewer. Even among HSAG-denied cases, six (9%) admissions would not have been referred to the physician reviewer by the nurse reviewer.

The SMH nurses were also asked to approve or deny each admission (Table 2). Of the 128 charts reviewed, the nurses would have approved 59 (46%) admissions and denied 69 (54%). Of the 64 HSAG-approved admissions, 23 (36%) would have been denied by the nurse reviewers, and 18 (28%) of the 64 HSAG-denied charts would have been approved. We have no way of comparing this result with HSAG review nurses, as they were not asked to make a final approval or denial decision.

Looking at only the 32 HSAG-approved cases (Table 3), agreement for approval was strong in 56% of cases, with either all reviewers or three of four agreeing. Disagreement was strong in almost half, however. In fact, two HSAG-approved cases would have been denied by all four SMH reviewers.

The 32 HSAG-denied cases were looked at in a similar manner (Table 4). Agreement for denial was strong in 63% of cases, with either all reviewers or three of four concurring. Disagreement was strong in the other 37%, however, with one HSAG-denied admission that would have been approved by all four SMH reviewers.

Table 5 summarizes the agreement or disagreement

TABLE 1.—*Admissions Approved and Denied by Scottsdale Memorial Hospital (SMH) and Health Services Advisory Group, Inc (HSAG) Physician Reviewers**

HSAG Physician Reviewers	SMH Physician Reviewers† Approved, No. (%)	Denied, No. (%)	HSAG Total, No. (%)
Approved	46 (36)	18 (14)	64 (50)
Denied	25 (20)	39 (30)	64 (50)
SMH total	71 (55)	57 (44)	128 (100)

*χ^2 13.9 ($P < .001$).
†Each of the 32 approved and 32 denied admissions was reviewed twice by different SMH physicians.

TABLE 2.—*Admissions Approved and Denied by Scottsdale Memorial Hospital (SMH) Nurse Reviewers and Health Services Advisory Group, Inc (HSAG) Physician Reviewers**

HSAG Physician Reviewers	SMH Nurse Reviewers† Approved, No. (%)	Denied, No. (%)	HSAG Total, No. (%)
Approved	41 (32)	23 (18)	64 (50)
Denied	18 (14)	46 (36)	64 (50)
SMH total	59 (46)	69 (54)	128 (100)

*χ^2 16.6 ($P < .001$).
†Each of the 32 approved and 32 denied admissions was reviewed twice by different SMH nurse reviewers.

TABLE 3.—*Admissions Approved and Denied by Scottsdale Memorial Hospital (SMH) Physician and Nurse Reviewers Versus Admissions Approved by the Health Services Advisory Group, Inc (HSAG)*

SMH Nurse Reviewer	SMH Physician Reviewer: Approved-Approved,* No. (%)	Approved-Denied,† No. (%)	Denied-Denied,‡ No. (%)	Nurse Total, No. (%)
Approved-approved	11 (34)	2 (6)	1 (3)	14 (44)
Approved-denied	5 (16)	7 (22)	1 (3)	13 (41)
Denied-denied	2 (6)	1 (3)	2 (6)	5 (16)
Physician total	18 (56)	10 (31)	4 (12)	32 (100)

*Both physicians or nurses approved the admission.
†One physician or nurse approved and one denied the admission.
‡Both physicians or nurses denied the admission.

TABLE 4.—*Admissions Approved and Denied by Scottsdale Memorial Hospital (SMH) Physician and Nurse Reviewers Versus Admissions Denied by the Health Services Advisory Group, Inc (HSAG)*

SMH Nurse Reviewer	SMH Physician Reviewer: Approved-Approved,* No. (%)	Approved-Denied,† No. (%)	Denied-Denied,‡ No. (%)	Nurse Total, No. (%)
Approved-approved	1 (3)	4 (13)	0	5 (16)
Approved-denied	0	6 (19)	2 (6)	8 (25)
Denied-denied	1 (3)	11 (34)	7 (22)	19 (59)
Physician total	2 (6)	21 (66)	9 (28)	32 (100)

*Both physicians or nurses approved the admission.
†One physician or nurse approved and one denied the admission.
‡Both physicians or nurses denied the admission.

TABLE 5.—*Admissions Approved and Denied by Scottsdale Memorial Hospital (SMH) Physician and Nurse Reviewers**

SMH Nurse Reviewer	SMH Physician Reviewer: Approved-Approved,† No. (%)	Approved-Denied,‡ No. (%)	Denied-Denied,§ No. (%)	Nurse Total, No. (%)
Approved-approved	12 (19)	6 (9)	1 (2)	19 (30)
Approved-denied	5 (8)	13 (20)	3 (5)	21 (33)
Denied-denied	3 (5)	12 (19)	9 (14)	24 (38)
Physician total	20 (31)	31 (48)	13 (20)	64 (100)

*χ^2 17.2 ($P < .002$).
†Both physicians or nurses approved the admission.
‡One physician or nurse approved and one denied the admission.
§Both physicians or nurses denied the admission.

among the study reviewers. All four reviewers agreed for either approval or denial in 21 (33%) admissions. Strong disagreement occurred in 17 (27%) cases where two recommended denial. Of note is that the two SMH physician reviewers disagreed with each other on 31 (48%) of the cases, and the two nurse reviewers disagreed on 21 (33%).

At the end of each review, the physicians were asked questions regarding the case (Table 6). In 115 of 128 charts reviewed, the SMH physician thought that the patients were admitted because of a genuine concern that a hospital stay was necessary. Even among SMH-denied cases, less than half of the reviewers thought that the patients were admitted hastily. Yet, in slightly more than half of the SMH-denied cases, the review physicians thought that patients were admitted for convenience.

Physicians from Scottsdale Memorial Hospital denied admission even though the reviewers thought the admitting physicians documented the need for admission adequately or maintained an accepted level of intensity of care. Thus, SMH physicians thought that denial was appropriate even though the patients met at least one of the criteria for admission. In five cases where the SMH physicians denied the admission, review physicians thought that care would have been compromised if the patient admissions had not taken place. It is presumed that these physicians followed the interpretation of the criteria more closely and made decisions based on those criteria rather than a sole concern for the patient. The reviewers thought the admitting physicians were clearly in error in less than half of the admissions denied by SMH physicians.

We attempted to determine how the review physicians would have treated a similar situation by asking them the following two questions (Table 6):

- Would you have treated this patient in your office, emergency department, nursing home, or other facility?
- Under similar circumstances, would you have admitted this patient?

These questions could be thought of as mutually exclusive. That is, if the review physician thought the admission should be denied, then treatment could have been given in an outpatient setting, and if the patient's admission was approved, then care was needed in the hospital. In 9 of the 71 SMH-approved patient admissions, the SMH physician reviewers would have treated the patient in an outpatient setting. In 13 of 57 denied cases, the physician reviewers would have admitted the patient under similar circumstances. From this we conclude that some physicians admit patients even when they realize that the admission may be denied.

For the 32 HSAG-approved admissions, the total hospital charges were $91,531 (average, $2,860), and for the 32 HSAG-denied admissions, the total charges were $81,731 (average, $2,554). The total hospital charges were $62,629 (average, $3,131) for the 20 cases wherein both SMH physicians approved the admission. In the 31 cases where the SMH physicians disagreed, the total charges were $81,204 (average, $2,619); and in the remaining 13 cases, where both physicians denied admission, the total charges were $29,430 (average, $2,264).

Discussion

The purpose of reviewing Medicare admissions is to reduce costs associated with inappropriate admissions while trying to maintain good quality of care for patients who legitimately require hospital admission. Our study points out a serious problem with the review process: despite objective criteria, much subjective variation exists. Many admissions that were approved by the Health Services Advisory Group were denied by practicing physicians, and many admissions that were denied by HSAG were approved by the study physicians. When two physicians reviewed each chart, they disagreed with each other almost half the time. These discrepancies have serious implications for hospital and physician reimbursement.

The cases in this study sorted into three distinct groups: those with strong agreement among reviewers for denial, those with strong agreement for approval, and those with strong disagreement among reviewers.

In cases where agreement for denial was strong, it can be assumed that the admission was indeed inappropriate or that

TABLE 6.—*Scottsdale Memorial Hospital (SMH) Physicians' Positive Response to Questions Related to Patients' Admissions**

	HSAG Reviewer			SMH Reviewer			
Question	*Approved, No. (%)*	*Denied, No. (%)*	*P Value*	*Approved, No. (%)*	*Denied, No. (%)*	*P Value*	*Total, No. (%)*
Was the patient admitted because of genuine concern that hospitalization was necessary?	60 (94)	55 (86)	NS	70 (99)	45 (79)	<.001	115 (90)
Was the patient hastily admitted without obtaining pertinent facts that could have prevented the admission?	8 (13)	21 (33)	<.01	3 (4)	26 (46)	<.001	29 (23)
Was the patient admitted for convenience?	17 (27)	21 (31)	NS	7 (10)	31 (53)	<.001	38 (30)
Was the need for admission adequately documented?	42 (66)	30 (47)	<.05	60 (85)	12 (21)	<.001	72 (56)
During the first 48 hours, was the intensity of care that the patient received appropriate for the admitting diagnosis?	44 (69)	35 (55)	NS	59 (83)	20 (35)	<.001	79 (62)
If admission had not taken place, would this patient's health care have been compromised?	42 (66)	18 (28)	<.001	55 (76)	5 (11)	<.001	60 (47)
Was the physician clearly in error in admitting the patient?	7 (11)	15 (23)	NS	0	22 (39)	<.001	22 (17)
Would you have treated this patient in your office, emergency department, nursing home, or other facility?	23 (36)	36 (56)	<.05	9 (13)	50 (88)	<.001	59 (46)
Under similar circumstances, would you have admitted this patient?	43 (67)	34 (53)	NS	64 (90)	13 (23)	<.001	77 (60)
Would you have consulted any additional physician(s) to care for this patient?	17 (25)	13 (20)	NS	14 (20)	16 (26)	NS	30 (23)
Total patients	64	64		71	57		128

HSAG=Health Services Advisory Group, Inc. NS=not significant

*Each of the 32 HSAG-approved and 32 HSAG-denied admissions was reviewed twice by different SMH physicians.

documentation was inadequate. In these cases, the peer review organization should specifically outline the reasons for denial. This would help educate the admitting physician and, it is hoped, would improve patient care and reduce the number of future denials.

In cases where agreement for approval was strong, it can be assumed that the admission was appropriate; either the case met the severity of illness and intensity of service criteria or other circumstances of the case were such that reviewers strongly agreed the admission was appropriate anyway. Costs to the peer review organization could certainly be reduced if fewer cases in this group were sent for physician review by the nurse reviewers. Identifying extraordinary circumstances or adding qualifiers to Medicare criteria may allow nurse reviewers to screen cases more effectively. Further research in this area would be helpful.

Cases where there was strong disagreement among reviewers present the greatest problem. This group represents up to a third of all reviewed charts. Reasons for these disagreements are many and probably include imperfect criteria, differences in reviewer bias and training, and the subjective nature of the practice of medicine. These cases could be unfairly denied admission if only one physician reviewer makes the decision, but having every chart reviewed twice by different physician reviewers would be too costly and burdensome. We suggest that all cases that are denied admission by a physician reviewer be reviewed independently and blindly by a second physician while reviewing his or her usual case load. This would allow a fair and unbiased review by two independent physicians and at the same time keep the overall cost of administering the program to a minimum. If both physicians deny admission independently, then a final denial can be stipulated. When there is disagreement, the two physician reviewers can resolve the final outcome between themselves or a third independent physician or panel can make the ultimate decision.

Because the written record serves as the sole means of making the decision of approval or denial, physicians who understand the criteria and who are skilled in written documentation have a distinct advantage over those who are not so skilled. If a physician clarifies the necessity for an admission, the review physician may be more likely to approve the admission even though absolute criteria for admission may not have been met. Yet, the admission of a similar case may be denied if the physician lacks the ability to document the need for admission. Medical staffs and continuing education programs need to emphasize good documentation in the medical record, as well as understanding of current admission criteria.

Most reviewers thought that the criteria were generally fair but often difficult to apply to a case being reviewed. Because a review is based solely on the medical record, it is difficult to evaluate the intangible factors of a patient's admission, such as the social, economic, and emotional well-being of a patient and family or a physician's intuition regarding the severity of the illness. Once again, documentation of a physician's reasoning or contributing circumstances may prevent unfair denials.

A final factor that likely contributes to a discrepancy among reviewers is reviewer bias. One reviewer may be dogmatic and strict in interpreting the criteria and another may possess a more caring or compromising set of values. What effect this has on approval or denial is difficult to evaluate, but peer review organizations should take measures to assure consistency among reviewers.

Cost-containment practices are fraught with problems. With rising costs, better expenditure of money needs to be achieved, but none of the measures taken should result in inferior health care. The methods for reducing health care costs must be just and equitable, not only to patients but also to physicians and hospitals. Peer review organizations need to be open-minded and receptive to physicians', hospitals', and patients' opinions and problems. The review process must be continuously evaluated, and the primary motivating factor is still the quality of care.

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Radiologic Case

A 46-Year-Old Woman With a Painless Movable Breast Mass

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 46-year-old woman felt a lump in her right breast. She visited her physician, who palpated a 5-cm mass that was painless, well-circumscribed, and movable. No skin dimpling or nipple retraction was present. A low-dose mammogram (Figure 1) was done, and this was followed by an ultrasound examination of the right breast (Figure 2).

What is the probable diagnosis?

How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A medial-lateral view of the right breast shows a large, well-circumscribed mass. (The metallic density is a marker placed over the palpable lesion.)

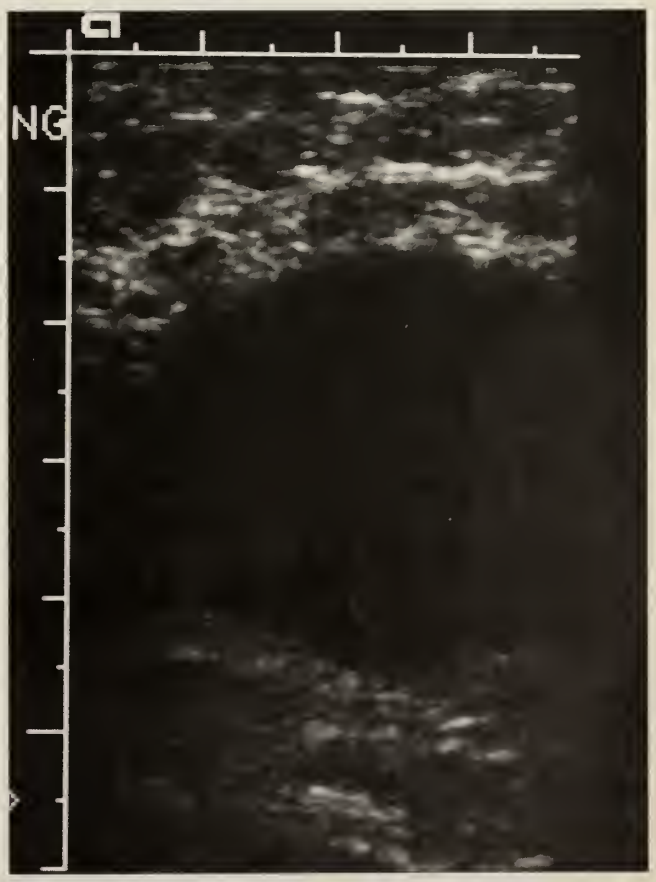

Figure 2.—An ultrasound examination of the mass shows a lack of internal echoes and equal echogenicity of tissue anterior and posterior to mass.

(Myers T, Stegman CJ, Crowe JK, et al: A 46-year-old woman with a painless movable breast mass. West J Med 1989 Jul; 151:97-98)

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DIAGNOSIS: Fibroadenoma of the breast

BREAST SELF-EXAMINATION, physician palpation, and x-ray mammography are proven and well-documented methods for the detection of breast cancer. While ultrasound examination of the breast has not proved to be a good primary modality, it has become increasingly more useful as a secondary procedure that can distinguish between cystic (benign) and solid (potentially malignant) masses. The sonographic evaluation of solid breast masses has limitations because benign and malignant masses may have the same appearance on an ultrasonogram. The separation of masses into cystic versus solid, however, has an accuracy approaching 100%. Sonography alone can, therefore, often establish the diagnosis of a benign cyst, eliminating the need for biopsy or frequent follow-up visits.

Sonographic characteristics of solid breast masses—and particularly fibroadenomas—can be highly variable. They can closely mimic cystic lesions on occasion, leading to an inaccurate diagnosis. Mistakes in diagnosis can be avoided by the stringent appraisal of critical sonographic criteria for differentiating solid from cystic lesions.

Diagnostic criteria for distinguishing breast masses by ultrasonography have been described by Cole-Beuglet and co-workers as follows:

Characteristics	*Cystic*	*Solid*
Contour	Smooth	Irregular to smooth
Shape	Round or oval	Variable
Internal echoes	None to few	None to hyperechoic
Anterior border	Strong	Strong to intermediate
Posterior border	Strong	Absent to strong
Distal echoes	**Enhanced**	Intermediate
Shadows	Lateral wall	Central interrupted
Attenuation	**Minimal**	Intermediate to great

Cysts characteristically are sharply defined, particularly on the posterior wall. Because they transmit sound better than surrounding tissue, they produce increased echoes deep or posterior to the lesion, as compared with the echoes immediately anterior to the mass. This property is called through-transmission and is the most important differentiating sign between a cyst and a mass. Internal echoes sometimes appear within cysts due to reverberations, partial volume effect, or turbidity of the cyst fluid, so that this is not a good differential criterion. A failure to show unequivocal sonographic signs of a cyst necessitates further workup. This can be a biopsy or cyst aspiration, which helps exclude a neoplastic lesion.

The lesion shown in Figure 2 is smoothly contoured and entirely anechoic internally. These findings suggest a cystic mass. The absence of good through-transmission (no increased echoes posterior to the mass), however, suggests that the lesion is solid in character, rather than cystic. A biopsy was taken of the lesion, and it proved to be a fibroadenoma.

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Information

The Professional Satisfaction of New Mexico Physicians

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A JOB SATISFACTION QUESTIONNAIRE was sent to 2,100 New Mexico physicians. A total of 410 (approximately 20%) responded. Respondents represented all the major medical specialties in the proportion that exists in practice in New Mexico. In all, 65% indicated that they were moderately or very satisfied with practice in the past two years, but 35% were mildly or very dissatisfied. Happiest were family practitioners, psychiatrists, and pediatricians; unhappiest were general surgeons and internists. Physician satisfaction by age showed a modest decrease for those between 45 and 54 years of age as compared with those a decade younger, and a further decrease was noted in those over 55.

The major source of dissatisfaction for 45% of all physicians in the study was the threat of malpractice and the high insurance premiums involved. A loss of control of patient care to third parties was the next-most-prevalent source of dissatisfaction (40%). Many physicians also mentioned the new stress of unpleasant competition between individuals and hospitals. By contrast, inadequate free time was the major frustration for women physicians (40%), with income too low for effort ranking second (38%). By practice type, medical school faculty (78%) and those working in multispecialty clinics (75%) indicated the greatest degree of satisfaction. Hospital-based physicians, such as radiologists, pathologists, and anesthesiologists, were relatively satisfied. Very few physicians seemed unhappy in the role of gatekeeper. Only 20% had seriously considered changing their specialty, but 45% of all responding physicians would leave medicine if they were financially independent. This figure is even higher for general surgeons (65%) and obstetrician-gynecologists (70%) (Figure 1).

General surgeons and orthopedists thought there were too many physicians being trained in their specialties, and family practitioners and internists thought the numbers were about right. A total of 58% of responding physicians indicated they would discourage college students from going into medicine, while 80% of obstetrician-gynecologists and 68% of general surgeons felt this way (Figure 2).

By far the most frequent recommendation for change was for organized medicine to support tort reforms in relation to malpractice problems.

Earlier studies of physician satisfaction, especially those of Mawardi,[1,2] showed entirely different patterns. Her study, which followed physicians from the Case Western Reserve University (Cleveland) graduating classes of 1956 through 1965 for several decades, indicated that physicians as a whole were content with their practices, and few said they would have chosen a different career. They were primarily stressed by time pressures of work and lack of leisure time. Only those practicing in California complained of any problem with malpractice suits, and none reported problems with patient care restrictions by third parties.[1] In her follow-up study of the same group in 1979, malpractice threats and premiums were on the minds of all respondents, and the adverse effect on physician-patient relationships was a related stress. Time pressures had been somewhat relieved by group practice arrangements.[2]

It seems, therefore, that the major sources of dissatisfaction for the physicians answering this questionnaire—that is, malpractice threats and premiums, third-party control of medical decisions, and the unpleasant competitive conflicts between individual physicians and hospitals—are related to changes in medical practice patterns in this decade. Although each person is ultimately responsible for his or her own happiness and job satisfaction, negative external factors can increase the difficulty in achieving this goal. Perhaps the nature of the above irritants requires organizational and political solutions that can only be initiated by professional societies and group action.

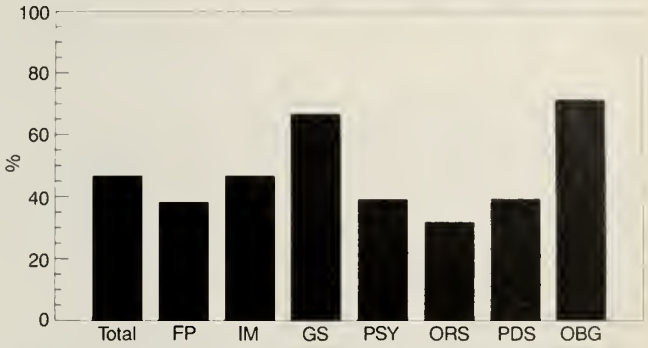

Figure 1.—The graph shows the percentage per specialty of physicians who responded that they would leave medicine if financially independent. FP = family practice; IM = internal medicine; GS = general surgery; PSY = psychiatry; ORS = orthopedics; PDS = pediatrics; OBG = obstetrics-gynecology

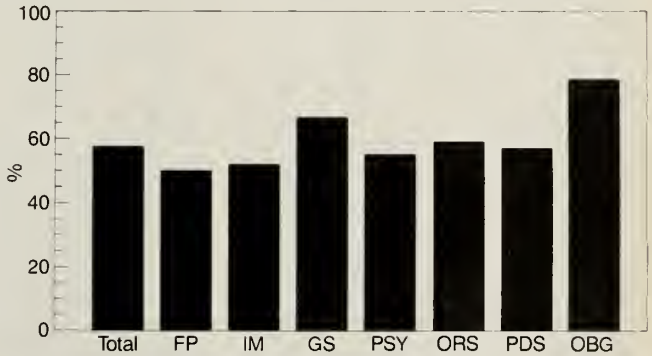

Figure 2.—The graph shows the percentage of physicians who would discourage college students from going into medicine. FP = family practice; IM = internal medicine; GS = general surgery; PSY = psychiatry; ORS = orthopedics; PDS = pediatrics; OBG = obstetrics-gynecology

(Edwards WS, Rezler AG, Pett S: The professional satisfaction of New Mexico physicians. West J Med 1989 Jul; 151:99)

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Lessons From the Practice

Illness as Crime

CLIFFORD I. HARRIS, MD, *San Francisco*

It was my first day as a fourth-year medical student. I was starting my rotation in Family and Community Medicine and, having heard about the relatively high degree of autonomy that I would be allowed in the clinic, I was an uneasy mixture of eagerness and dread. I had been given my own office with the ambiguous "Harris, M.S." written in felt pen on the door's nameplate. I sat and clicked my stethoscope from bell to diaphragm and back until the nurse knocked.

"We've got a great patient for you. Sounds like a new onset diabetes. . . ."

As I followed her down the hall, I thought, "No problem: polyuria, polydipsia, polyphagia. Probably diet and oral hypoglycemics, maybe insulin."

My patient, Mr P., was a tall, handsome man who offered a warm handshake and a nervous smile. He had come with his wife, who looked restless and clearly the more worried of the two. As we walked back to my office, the history of their lives and of his recent illness poured out from her. They had emigrated a few years earlier from the Middle East, where she had worked as a nurse. Now, he was the sole breadwinner for them and their children. She described his symptoms of urinary frequency, 20-pound weight loss, increased hunger and thirst. He added only that he was concerned that he had cancer, since his father had lost weight before dying of a tumor.

Mrs P. sighed and asked in a hushed voice, "It's diabetes, isn't it, Dr Harris?"

I agreed that his symptoms were indeed classic but said that we would have to run some tests. After the physical examination, we did a finger stick and waited as the little computer deliberated and then pronounced its verdict: 352.

"That certainly is strong evidence that you have diabetes, Mr P.," I said. And then it started.

Mrs P. began to list her husband's virtues to me as if I were a criminal judge and she his lawyer: He was a good, honest, hard-working man; he was good to the children; never said a cruel word to anyone; he was clean and punctual. Her eyes welled up and her voice tightened as she pleaded. And I realized that she must have seen end-stage diabetic complications in her own patients. She saw me as a last resort to save her from the realization of her fears, as if I could preserve his eyes and kidneys with an act of mercy or had saved my special cures for the clean and punctual.

Mr P., however, was relieved; to him, diabetes was something quite tolerable. His dentist had it, he said. And it was not cancer. I was a little perplexed by Mrs P.'s reaction and tried to reassure them both that I thought he had not earned his disease by some wrongdoing.

Since that day, I have seen Mr P. four times in follow-up appointments, sometimes alone, sometimes with his wife. He is now managed on an oral hypoglycemic; that was the simple part.

The challenge was to understand what had motivated Mrs P.'s response. Clearly, she shows strong denial and a sense of vulnerability. But what stands out for me is something that I had heard about and had to see to appreciate: patients and families can perceive illness as punishment and as the crime itself, something to feel guilty about or ask forgiveness for. The recent AIDS epidemic is an obvious example of this and also shows that not only a patient but also a patient's society can play a role in blaming the victim.

Mrs P. was blatant about her feelings and I hope the issue will be more apparent with AIDS patients, but I wonder how much unnecessary suffering is added to illness by more covert feelings of self-blame. The psychological basis of this phenomenon may be complex, but it seems simple enough to consider asking patients how they feel about their diseases. The amount that can be done to preserve Mr P.'s eyes and kidneys is debatable, but it is certainly within the power of a physician to act as a resource for patients to avoid compounding their illness with unnecessary emotional pain.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Harris CI: Illness as crime. West J Med 1989 Jul; 151:100)

When this article was written, Dr Harris was a fourth-year medical student at the University of California, San Francisco, School of Medicine. He is now an intern in pediatrics at Childrens Hospital of Oakland, California.

Reprint requests to Clifford I. Harris, 791 Ashbury St, San Francisco, CA 94117.

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Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, pennatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects – Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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INTERNIST seeks BC/BE partner for historic rural area. Bustling practice with limitless opportunity serving Washington state island community. Safe and scenic. Convenient tertiary centers for referral and CME. Full service local hospital. Send résumé to PO Box 840, Coupeville, WA 98239.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

GENERAL SURGEON. Established young, mellow but compulsive General Surgeon in southern California seeks an associate so he can spend more time with his young children. If interested send CV and personal description to Number 159, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

EMERGENCY PHYSICIAN. Los Angeles area. Active base station, community hospital, fee-for-service. Malpractice, etc. Dynamite opportunity. Call for details. Dr Murchison, (714) 627-6111, ext 300.

ROSEVILLE. Immediate opening for BC/BE Family Practitioner. Ours is a satellite clinic in a group model HMO. Practice is primarily adult care with no OB or night call. Attractive salary, comprehensive benefit package, opportunity for shareholder status available. Malpractice provided. Contact Richard Fury, MD, The Permanente Medical Group, Inc, 1001 Riverside Ave, Roseville, CA 95678; (916) 784-4620.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful ambulatory health care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE primary care specialists preferred. Contact Bob Morris, MD, FACEP, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering start-up in personal private practice. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Pediatrics, General Surgery (breast disease focus), OB/GYN. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Dr Larry W. Hirons, Medical Director
1162 Willamette St
Eugene, OR 97401

(Continued on Page 106)

(Continued from Page 105)

PHYSICIANS WANTED

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee-for-service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is in the second phase of an ambitious development plan and is searching for physicians residency trained in Emergency Medicine. The Health Sciences campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level I trauma center, has paramedic base station training responsibilities, and has a helicopter service. Emergency Physicians supervise medical students, interns, and residents in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

PHYSICIANS WANTED

FAMILY PRACTICE/INTERNAL MEDICINE/OB/GYN

Attractive opportunities for BC/BE physicians in a variety of settings in the *Midwest* (many on lakes). Contact Bob Strzelczyk to discuss *your* practice requirements and these positions. ***STRELCHECK & ASSOCIATES, INC,* 12724 N. Maplecrest Ln, Mequon, WI 53092; 1 (800) 243-4353.**

SACRAMENTO, CALIFORNIA. Part-time, semi-retired Orthopedic Surgeons and Neurosurgeons needed as independent medical examiners. Limited treatment, if desired. Flexibility in scheduling. Lucrative fee-for-service. California license and BC required. Reply to Number 158, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

INTERNIST for busy, well established, multispecialty group experiencing ongoing expansion. Competitive salary, liberal fringe benefits. Send CV to Mark Cole, MD, The Permanente Medical Group, 1200 El Camino Real, South San Francisco, CA 94080. EOE.

LAS VEGAS, NEVADA. Family Physician needed to anchor new multispecialty clinic. Upscale suburban location. Ground floor opportunity of unlimited potential. Contact Patrick Schmidt, 250 Regency Ct, Waukesha, WI 53186; 1 (800) 338-7107.

NURSE PRACTITIONER wanted to start August 15, 1989. California State University, Stanislaus Student Health Center, Turlock, California. 12 minutes south of Modesto, California. Excellent working environment. Permanent position (10 months per year/paid for 12 months). Salary $2,060 to $2,480 per month plus benefits. Call Larry Wragg, MD, Director of Student Health Services, Personnel Department, (209) 667-3351, or write Personnel Department, California State University, Stanislaus, 801 W. Monte Vista Ave, Turlock, CA 95380.

NEUROLOGIST to join state-of-the-art Neurology center in Minnesota. Excellent electrodiagnostic facility and regionally acclaimed neuroradiology department. Supportive referral base. Contemporary lakeshore office space connected to hospital via skywalk. Call/coverage available. Community offers superb quality of life, low crime rate, and cultural and recreational amenities including boating, hunting, fishing, skiing, and access to universities. Contact Bryan Bassett, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

NEWPORT BEACH, CALIFORNIA. Fashion Island, Obstetrician/Gynecologist needed to join thriving solo private practice in this luxurious southern California community, position available immediately. PO Box 357, Newport Beach, CA 92662.

BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

(Continued on Page 109)

How many times have you reluctantly declined dinner with friends because of professional commitments?

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Enjoy a week, a year or a career with the flexibility and benefits of the *locum tenens* lifestyle.

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STOP LESIONS FROM SURFACING

An alarming rise in the incidence of genital herpes points to the need for better disease treatment. Fortunately, long-term maintenance therapy with ZOVIRAX® can help keep herpes patients lesion-free. In controlled studies of 4 to 6 months' duration, recurrences were totally prevented in up to 75% of patients. And during two years of clinical use, daily therapy has been shown to be generally well tolerated.[1] One capsule TID...the best way to stop lesions from surfacing.

Reference. 1. Data on file, Burroughs Wellcome Co.

ZOVIRAX®
(acyclovir) **capsules**

Keeps herpes patients lesion-free longer

Please see brief summary of prescribing information on next page.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

Burroughs Wellcome Co.,
Research Triangle Park,
North Carolina 27709

ZOVIRAX®
(acyclovir) capsules

Daily therapy helps keep patients lesion-free longer*

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy, the severity of subsequent episodes and the effect on the natural history of the disease are still under study

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day No effect upon implantation efficiency was observed when the same dose was administered intravenously In a rat peri- and postnatal study at 50 mg/kg/day s c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis Testicles were normal in dogs given 50 mg/kg/day i v for one month

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p o), rabbit (50 mg/kg/day, s c and i v) or in standard tests in the rat (50 mg/kg/day, s c) In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat The clinical relevance of these findings is uncertain There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13 1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3 6%), and arthralgia in 9 of 251 (3 6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules) Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1 73 m^2

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56)

Store at 15°-30°C (59°-86°F) and protect from light and moisture

U.S. Patent No 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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North Carolina 27709

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(Continued from Page 106)

PHYSICIANS WANTED

Medical Director
In the Heart of San Bernardino County

Young, rapidly expanding 13-physician multi-specialty group seeks experienced medical director. Must be a leader with excellent interpersonal skills, high standards, strong HMO/UR background, and BC in primary care specialty. Clinical-60%; administrative-40%. Strong administrative team; excellent compensation package. New hospital. Outstanding community choices.

Leon Pettijohn, VP
Pacific Physician Services
(714) 887-1444

PUBLIC HEALTH DIRECTOR. Maricopa County is seeking a physician licensed in Arizona, or eligible, to direct a division of an integrated health care system serving a population of over two million. Position requires Master's degree in Public Health and a minimum of five years' experience in Public Health Administration. $75,400 to $86,700 annual salary. Please send résumé by July 28, 1989, to Maricopa County Personnel, Health Services Division, PO Box 5099, Phoenix, AZ 85010. EOE.

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIANS WANTED

WANTED BC/BE PEDIATRICIANS

Nighttime pediatrics clinic. For information see article in *Contemporary Peds*, July 1987. Part-/full-time 20 to 40 hours per week. Salary negotiable. Inquire c/o

Jed Dunford
279 East 5900 South
Murray, UT 84107

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, General Surgery, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

PHYSICIANS WANTED

FAMILY PRACTICE, INTERNAL MEDICINE, OB/GYN, URGENT CARE, ORTHOPEDICS, PEDIATRICS, ENT, NEUROLOGY

and other specialties, immediate opportunities for BC/BE physicians in California, Midwest, and southern states. Also private practices available in northern and central California. Send CV or call **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762 or FAX to (415) 376-0813.**

BC/BE INTERNIST being recruited for the community of Artesia, New Mexico. Solo practice with cross-coverage available from local Internist. Community-based financial assistance may be available for the right individual. Family oriented community with year round recreation; excellent weather. Fully equipped 38-bed hospital. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PEDIATRICIAN BC/BE. Join two Pediatricians and nurse practitioner in busy, quality practice in rapidly growing community near Sacramento, California. Excellent community hospital and quality of life. Five person call schedule. Send CV to The Childrens Medical Clinic, 729 Sunrise Ave, #602, Roseville, CA 95661.

PHOENIX—GERIATRICIAN. A regionally recognized, multispecialty group here is now seeking a BC Geriatrician to provide ongoing support for their many patients. Send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-7A, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

UTAH—FAMILY PHYSICIAN. A young, BC Family Physician is seeking an associate to join him in opening a new office in an underserved growth area five miles from our 110-bed hospital in Layton, Utah, which serves a population of 140,000. A competitive financial package will be offered with opportunity for partnership. Layton is located 15 miles north of Salt Lake City and 12 miles south of Ogden. An undisturbed natural environment offers a variety of outdoor activities, while education and family life are highly emphasized. Send CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-7B, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

FAMILY PRACTICE. California BC/BE Family Practice Physician sought by large medical group for a rural satellite location 15 miles from Sacramento. Competitive salary and benefits first year. For more information, please send current CV to Warren J. Boyer, Jr, MD, Marysville Medical Group, 800 Third St, Marysville, CA 95901.

PROGRAM DIRECTOR, FAMILY PRACTICE RESIDENCY PROGRAM. Contra Costa County, Martinez, California, is seeking a qualified, BC Family Physician to direct our mature, thriving residency. This is a well established, University of California, Davis affiliated, solo residency program which offers residents rigorous clinical training in preparation for careers working with underserved populations. Our program is set in a busy, family practice oriented county system on the outskirts of the San Francisco bay area. Terms negotiable. Please send letter of interest and CV to Lois Ellison, Residency Director Search Committee, Contra Costa County Health Services, 20 Allen St, Martinez, CA 94553. Contra Costa County is an Equal Opportunity/ Affirmative Action Employer.

SKI COUNTRY

BC/BE Family Practice Physician wanted for full-time faculty position. Must be willing to do OB. Prior teaching experience preferred. Opportunity to be involved in development of innovative rural health training. Contact **Dr Daniel Dill, 2333 N. 6th, Grand Junction, CO 81501; (303) 244-2195.**

PHYSICIANS
Ambulatory Care Clinic
CALIFORNIA

JSA, Inc., an internationally recognized healthcare management and consulting organization, is offering physicians full and part-time positions in a challenging and busy Family Practice/Primary Care Clinic located in San Diego, CA.

The following generous benefit package is offered to Physicians:

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Paid malpractice insurance**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

Qualifications include Board Certification in Family Practice, Pediatrics or a Primary Care Specialty, current state licensure and ACLS/BCLS.

For additional information, please contact: Susan Bray, Recruiting Director, JSA, Inc., Box 1305, Columbia, MD 21044. (301) 964-2811.

JSA, Inc.

An Equal Opportunity Employer

(Continued on Page 110)

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PHYSICIANS WANTED

RADIOLOGIST WANTED. Progressive hospital located at the foot of the Big Horn Mountains. Quality life-style, excellent hunting, fishing, and recreation area. Skills required in diagnostic, ultrasound, mammography, nuclear medicine, and CT. For information contact Howard Megorden, Administrator, Washakie Memorial Hospital, PO Box 700, Worland, WY 82401; (307) 347-3221.

ORANGE COUNTY, CALIFORNIA—FAMILY PHYSICIAN/INTERNIST. A Family Physician is needed to join an extended hours/private practice clinic in the Huntington Beach area with buy-in option after first year. Also, several busy solo Family Physicians in Anaheim and Westminster are seeking associates. Send CV to Manager, Professional Relations, Humana Inc, Dept HH-7C, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

SOUTHERN CALIFORNIA—OB/GYN. A busy, expanding group of two BC OB/GYNs, practicing in a Los Angeles County community of 115,000 for the past seven years, is now seeking to add a third member. For more details send CV to Manager, Professional Relations, Humana Inc, Dept HH-7D, 500 W. Main St, Louisville, KY 40201-1438, or call toll-free 1 (800) 626-1590.

STAFF PHYSICIAN. General/Family Practice. Northern California clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No Obstetrics. No Surgery. Near mountains, close to Sacramento, two and one-half hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Contact Jackie Travis, 938 14th St, Marysville, CA 95901; (916) 741-6245.

REGIONAL MEDICAL CENTER seeking quality oriented peripheral Vascular Surgeon as part of expansion into Vascular and Cardiac services. Draw area of 200,000. Active referral base generating estimated 450 vascular cases per year. 175-bed hospital offering excellent facilities including fully equipped Radiology department, lab, and private recovery rooms. Enjoy lush green, college community free from traffic, smog, and crime. Located on banks of Platte River. Area boasts outstanding hunting, fishing, and outdoor recreational amenities. Mountain getaways in Colorado Rockies only a day's drive away. Excellent compensation and long-term potential. Contact Bryan Bassett, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

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(209) 476-3013

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Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

PATHOLOGIST. AP-CP to join three BC AP-CP with special competence, certified in Dermatopathology, Immunohematology, and Immunopathology. 300-bed progressive acute care hospital. Adding a fourth Pathologist due to workload. Must have or be willing to develop a forté in Microbiology in addition to sharing AP workload. State-of-the-art medicine. All medical and surgical subspecialties represented. Boise, Idaho's capital city, has an enviable four season climate with abundant recreational outlets. World class fine arts center. Four year college with large stadium and sports pavilion. Downtown parks and river known for float trips and fishing. Six double chair lift skiing 16 miles away. Excellent schools. Great place to raise a family. Competitive income. Desire recently trained individual. All details first letter. No phone calls please. Reply to John C. Day, MD, 190 E. Bannock, Boise, ID 83712.

PEDIATRICIAN. BC/BE physician to join seven member Pediatric department in 55-physician multispecialty group. New medical building with inhouse ancillary services, urgent care center, and surgery center. Competitive salary, excellent benefits including partnership opportunity. Please send CV or contact Susan Smit, Director, Practice Development, Harriman Jones Medical Group, 2600 Redondo Ave, Long Beach, CA 90806; (213) 988-7062.

MD NEEDS NATIONWIDE. Family Practitioners, General Practitioners, Internal Medicine, OB/GYN, operating room, and other subspecialties needed for private groups and associations. Len Nugent and Co, 1556 Halford Ave, Ste 181, Santa Clara, CA 95051; call (408) 984-8293.

SAN FRANCISCO PRIMARY CARE AND HIV. Internist featured in *American Medical News* series on the private practice of AIDS is seeking a recent BC/BE Internal Medicine graduate, with HIV experience and/or training, who is empathetic, committed, computer literate, and willing to work most evenings and alternate weekends in a new office with panoramic San Francisco city and bay views. Salary guarantee $50K with percentage, benefits, and goal of partnership. Send cover letter and CV to Bill Owen, MD, 45 Castro St, Ste 402, San Francisco, CA 94114.

LOOKING FOR INTERNIST/FAMILY PRACTITIONER to join five physician group in Truckee, California. Northern Sierras at elevation 6,000 feet. Abundant recreation summer and winter—beautiful Lake Tahoe, restaurants, and skiing. 40-bed hospital with six ICU beds. Contact R. B. Ganong, MD, PO Box 2649, Olympic Valley, CA 95730; (916) 583-5320.

PSYCHIATRIST, Northern Arizona University. Progressive, accredited student health center is seeking a 10 month Psychiatrist to initiate mental health program. Northern Arizona University is situated in beautiful, mountainous Flagstaff, Arizona. Medical facilities for 13,000 students are located in the modern, spacious health center. Position available August 1989. Please address inquiries to Leonard A. Wright, MD, Director, PO Box 6033, Flagstaff, AZ 86011. NAU is an AA/EOE. Women and minority applicants are encouraged to apply.

WESTERN MONTANA. Family Practice Physician wanted to join two physician office practice. Nice, well equipped office. No OB or surgery. Women encouraged to apply. Full-time or part-time. Excellent schools, beautiful area, 25 minutes to major medical area. Reply to Number 163, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PHYSICIAN OR PRIMARY CARE INTERNIST to join a progressive network of community health centers serving an ethnically diverse population in Salt Lake City. If Family Practitioner, perinatal skills required; if Internal Medicine, interest in providing clinical leadership in Geriatrics or AIDS is desirable. Teaching opportunities with university Family Practice residency accompany this position that offers excellent salary/benefits and extraordinary recreational possibilities. Send CV to Stephen Ratcliffe, MD, 330 North 1300 West, Salt Lake City, UT 84116; (801) 328-5750.

FAMILY PRACTICE, NORTHERN CALIFORNIA. Immediate opening. Competitive salary. Excellent benefits. Malpractice provided. Contact Debra Pahl, CTHP, 564 S. Dora St, Ste D, Ukiah, CA 95482; (707) 468-5341.

(Continued on Page 112)

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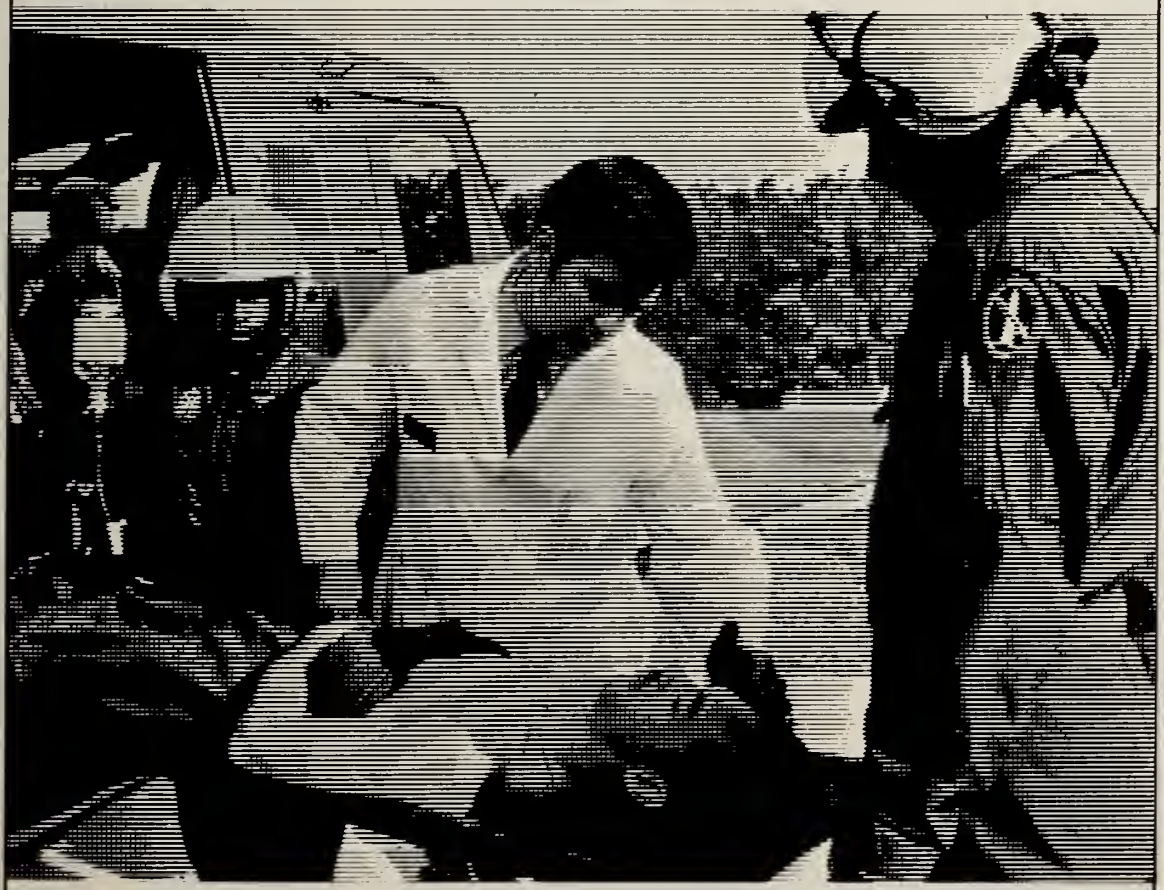

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(Continued from Page 110)

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Interviewing for an INTERNIST, an ORTHOPAEDIST, and a PSYCHIATRIST to take challenging and well-remunerated positions with an *ethical* new multispecialty clinic in Culver City devoted to quality care and opinion in the Worker's Comp field, starting September 15, one to two days a week, defense/AME/IME. Expert training in WCAB med/legal reporting required. Must be BC/BE and willing to look at each case comprehensively. This is not a mill.

Call or send CV to

David Melamed, MD
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507 Glenrock, Ste 304
Los Angeles, CA 90024
(213) 208-5035

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

BC/BE INTERNIST being sought to establish practice in resort community of Ruidoso, New Mexico. Beautiful mountain setting with easy access to all forms of recreation. Financial assistance may be available for the right individual. For more details, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

INTERNIST. BC/BE Internist wanted to join Internal Medicine group practice. Competitive salary and excellent fringe benefits. Early partnership. Send CV to Number 162, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602, or call Sara Brenner, (213) 478-5913.

NEUROSURGERY OPPORTUNITY in central California city of 175,000, with service area of 350,000, nestled in the San Joaquin Valley. 226-bed, modern and financially stable facility with 80 percent to 90 percent daily census. State-of-the-art neurosurgical operating facilities and equipment. Build high volume practice in underserved neurosurgical area. Enjoy outstanding recreational and cultural amenities in family oriented community. $150,000 to $200,000 net guarantee including all start-up, overhead, interviewing, and relocation expenses. Contact Timothy Donohue, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-5530.

PHYSICIANS WANTED

EXCEPTIONAL RHEUMATOLOGY PARTNERSHIP OPPORTUNITY to join successful group of Internists. Subspecialties within group include Oncology, Bronchoesophagology, Endoscopy, and Cardiology. College community of 35,000 on Nebraska's Platte River offers excellent quality of life with recreational, cultural, and social amenities. Generous financial package including first year salary, incentive plan, and benefits. Contact Bryan Bassett, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

INTERNAL MEDICINE PARTNERSHIP OPPORTUNITY to join well established multispecialty group in beautiful Lincoln, Nebraska. Clinic boasts advanced Radiology department and progressive certified lab. Recognized resources for open heart surgery, transplants, and Neurosurgery. Be busy immediately. Enjoy time off and easy one in four call. University town offers culture, shopping, dining, and sporting events not usually found in city of 190,000. Omaha is less than an hour away and offers big city amenities. Generous salary of $75,000 plus bonus and benefits offered for two-year term. Physician will receive highly coveted University of Nebraska "Big Red" season tickets. Contact Bryan Bassett, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

SACRAMENTO KAISER PERMANENTE. BE/BC Family Practitioners needed to join 23 Family Practitioners in large prepaid multispecialty group with excellent consultant support. Excellent financial package with no billing or practice management headaches. Reasonable working hours. Outstanding opportunity for well qualified candidates. Send CV to Stuart Hahn, MD, The Permanente Medical Group, 3240 Arden Way, Sacramento, CA 95825. EOE.

CHALLENGING POSITION FOR FAMILY PRACTITIONER/INTERNIST with Pediatrics/Gynecology background in Refugee Health Clinic. Duties include family oriented primary care, clinical consultation for nurse practitioners, participation in program development; may include consultation in school based teen health clinics; leadership/communication skills, and strong interest in cross cultural medicine essential. Interest in adolescent health desirable. Competitive salary, excellent benefits. Minorities encouraged to apply. Close date July 14, 1989. Contact Patsy Kullberg, MD, Multnomah County Health Division, 426 SW Stark St, 8th Floor, Portland, OR 97204; (503) 248-3674.

GENERAL PRACTICE—SOUTHEAST WASHINGTON. 32 physician multispecialty clinic needs full-time physician as second physician in Immediate Care Center. Center is part of main clinic and has full range of ancillary and consultative services available. Abundant free time with no on-call responsibility. Excellent school system. Outstanding recreational and cultural opportunities. Guaranteed salary with excellent fringe benefits. Contact Robert Caudill, MD, or David Maloney, Administrator, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720.

FAMILY PRACTICE—INTERNAL MEDICINE. A comprehensive multispecialty clinic in sunny San Diego seeks a full-time Internist/Family Practitioner for inpatient and outpatient care. Competitive salary. Excellent benefits. Attractive living environment. Send CV and three references to Dr Jairo Romero, 1971 Wildbrook Pl, Chula Vista, CA 92013; (619) 421-8149.

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BC/BE FAMILY PRACTITIONER sought to join an established practice in Albuquerque, New Mexico. Please send CV to Kathryn M. Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8338.

BC/BE INTERNIST sought to join an established practice in Albuquerque, New Mexico. Please send CV to Kathryn M. Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8338.

BC/BE GENERAL INTERNIST to associate with growing established Internal Medicine practice in beautiful Sierra foothills. Convenient to Sacramento, mountain resorts, and South Lake Tahoe. Progressive medical community with most specialties represented. Excellent, well staffed and equipped hospital. New medical complex being built in fastest growing area of county. Compensation negotiable. Early partnership. Subspecialties of Infectious Disease or Pulmonary would be welcome. Reply Frank D. Irwin, MD, 3420 Coach Ln #1, Cameron Park, CA 95682.

EMERGENCY PHYSICIAN to join established group at attractive, well-equipped emergency room, with excellent nursing, attending staff, in San Francisco. Malpractice paid. Contact Rob Hemmick, MD, St Mary's Hospital, 450 Stanyan St, San Francisco, CA 94117; (415) 750-5700.

MEDICAL ADMINISTRATOR (BILINGUAL) to supervise and coordinate activities of workers in the medical office. Will not be required to examine or treat patients, only provides information in the absence of the examining physician. Must be able to speak Farsi language. Must have medical degree and three years experience as a medical administrator or medical doctor. Salary $4,500 per month. Job site Los Angeles, California. Send this ad and résumé to Job # MV 0521, PO Box 9560, Sacramento, CA 95823-0560, not later than August 7, 1989.

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(Continued on Page 114)

SPECIAL ISSUES

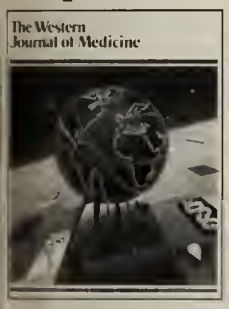
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

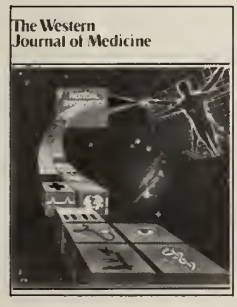
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



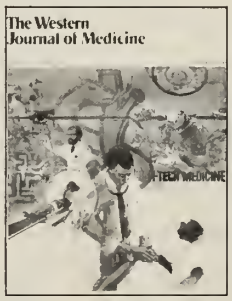
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



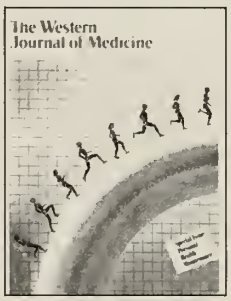
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



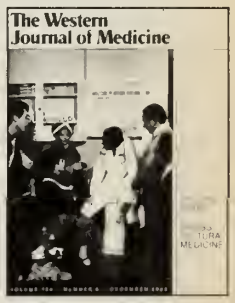
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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(Continued from Page 112)

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OPHTHALMOLOGIST, full- or part-time, for association or purchase of busy, active General Ophthalmology practice including office building, and equipment including lasers, computer, and automated equipment. Retina preferred, but not essential (no retinal specialist for 150,000 drawing population). Beautiful central California, one hour from Yosemite, and two hours from San Francisco and Monterey. Immediate need. Reply to Number 153, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SUCCESSFUL GENERAL PRACTICE FOR SALE in Santa Fe, New Mexico. Specializing in pain management. Telephone (505) 982-6827 evenings or weekends.

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GROWTH AREA OF SANTA CLARA VALLEY. New medical office space for lease in the growth area of Silicon Valley, Morgan Hill, California. Easy access, abundant parking, well located, generous tenant improvement allowances. Excellent patient referral sources. Contact Dr Jon Hatakeyama, (408) 779-7391.

WENATCHEE, WASHINGTON. Medical office for lease or sale. East of the Cascades, on the Columbia River. Well situated medical office suitable for two or three Internists, Family Practitioners, or other small group. 2,700 to 3,250 square feet. Air conditioned. 19 space parking lot. Available September 1, 1989. Write Arthur L. Ludwick, MD, 841 Red Apple Rd, Wenatchee, WA 98801 or phone (509) 663-3816.

OFFICE AVAILABLE, NORTH IDAHO. Opportunity to take over office of solo practitioner who is moving. No sale involved. Medical lab adjacent to office. Located in residential area in Coeur d' Alene, beautiful city by the lake. Call John McHugh, (208) 667-2591.

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MEETINGS

SIXTH SANTA FE COLLOQUIUM ON CARDIOVASCULAR THERAPY: Contemporary Treatment of Cardiac Arrhythmias
October 5-7, 1989, Santa Fe, New Mexico

Fees: $325 for ACC members; $390 for non-members; $205 for residents, fellows-in-training, nurses, and technicians. 16 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636; in Maryland, (301) 897-5400.**

CARDIOLOGY UPDATE—1989
October 12-14, 1989, Monterey, California

Fees: $375 for ACC members; $440 for non-members. 10.5 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636; in Maryland, (301) 897-5400.**

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TWO CONTINUING EDUCATION PROGRAMS FOR GENERALISTS AND INTERNISTS

Family Practice: Caring and Curing, January 20-25. Pain Management: Compleat Approach, January 26-28. Contact **Academy for Continuing Education of Kauai, PO Box 457, Kalaheo, HI 96741.**

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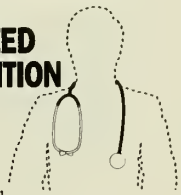

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SYMPOSIUMS

NATIONAL SYMPOSIUM ON MOLECULAR EPIDEMIOLOGY
October 14, 1989

Kern Medical Center, California State University, Bakersfield, and Kern County Health Department will hold a symposium on "Molecular Epidemiology—A New Tool in Investigating Childhood Cancer Clusters," at Dore Theater, CSUB. Specific topics will include:

- Monitoring Human Exposure of Carcinogenesis and Mitogenic Agents
- Biologic Markers in Environmental Epidemiology
- Genetic Testing and Chromosomal Studies in Childhood Cancer
- Genetic Screening and Monitoring High-Risk Populations

Members of the medical and scientific community, governments and industry are invited to participate.

For further information, contact:

Sheldon Freedman, MD
Symposium Chairman
Kern Medical Center
1830 Flower St
Bakersfield, CA 93305
(805) 326-2256

(Symposium Co-Chairmen: Paul Dhariwal, MD, and Hans Einstein, MD)

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1990, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1990, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-29, 1989, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1990, date and location to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1990, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 13-15, 1989, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 28-October 1, 1989, SEATAC Red Lion, Seattle.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1990, date and location to be announced.

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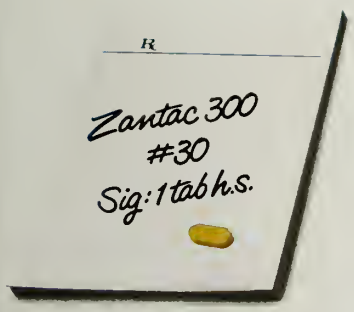
In active duodenal ulcers

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets



ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

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3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac 300

ranitidine HCl/Glaxo 300 mg tablets

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Glaxo / ROCHE

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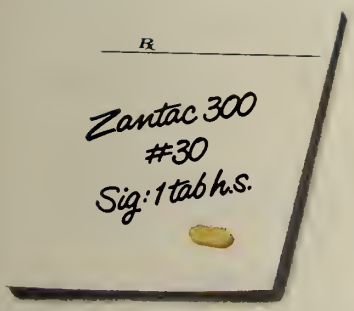

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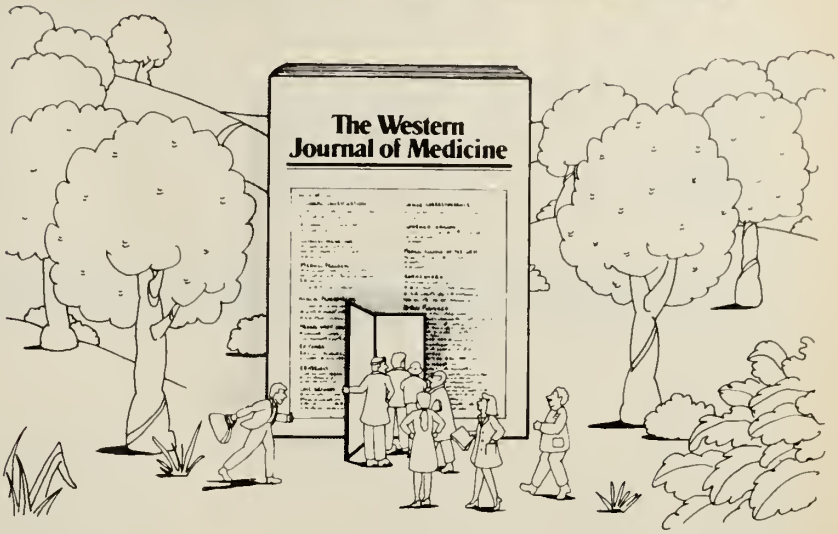

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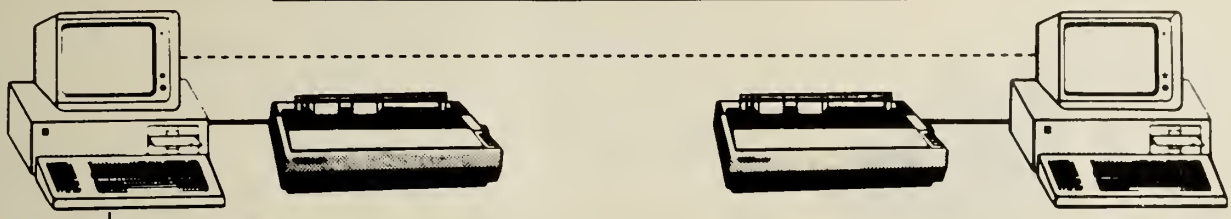

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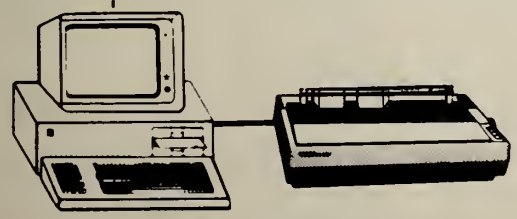

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A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: *General.* Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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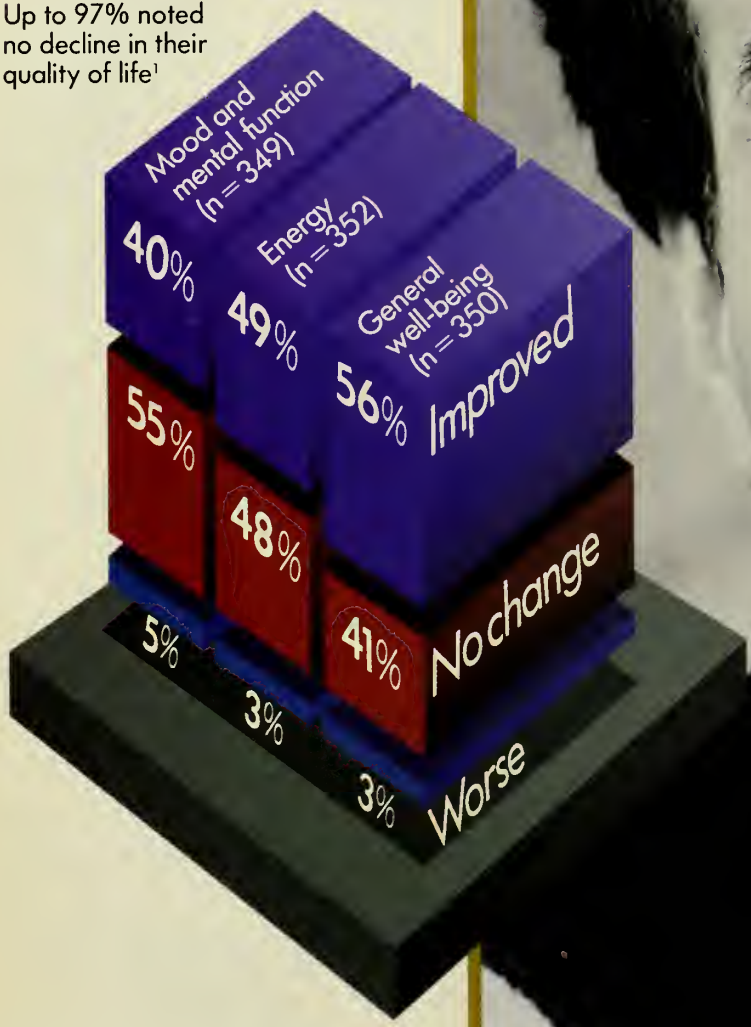

Self-assessment in an open study of newly diagnosed patients who had taken Calan SR for 12 weeks. "Improved" rating included responses of "improved" and "somewhat improved." "Worse" rating included responses of "worse" and "somewhat worse."

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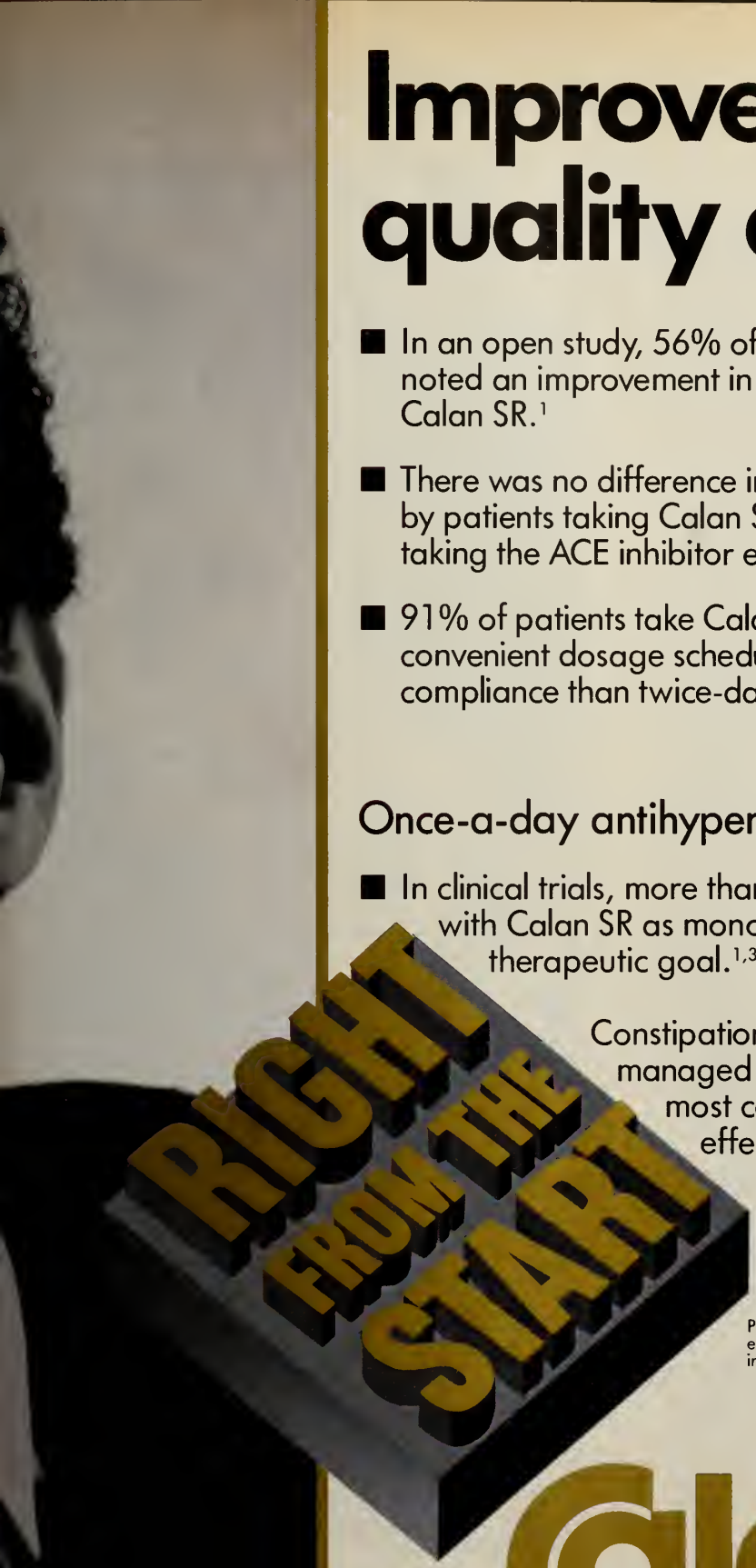

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence. 5/9/88 • C88-W5282V-1

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YOCON®
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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

August 24—**Interventions (in Alcohol and Chemical Dependency).** Benson Hospital, Benson. Thurs. Contact: Judy Doan, (602) 287-4722.

August 24—**Genetics Update.** Flagstaff Medical Center, Flagstaff. Thurs. Contact: H. Eugene Hoyme, MD, (602) 795-5675 (Tucson) or William Austin, MD, (602) 774-1811 (Flagstaff).

September 12—**Depression in the Elderly.** Holy Cross Hospital, Nogales. Tues. Contact: Judy Doan, (602) 287-4722.

September 13-April 11—**Cochise County Medical Society CME Mini Series.** Monthly. Contact: Continuing Medical Education, (602) 626-7832.

September 21—**Geriatric Grand Rounds—Kenneth Brummel-Smith, MD.** St Mary's Hospital, Tucson. Thurs. Contact: Gail Kreshner Riggs, (602) 626-6854.

September 22-23—**Cancer Reviews.** Orangetree Golf Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

September 28—**Family Systems (in Alcohol and Chemical Dependency).** Benson Hospital, Benson. Thurs. Contact: Judy Doan, (602) 287-4722.

October 14—**Practical Management of Common Cardiovascular Problems.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 3-4—**Neuro-oncology and Stereotactics: Current Approaches to CNS Neoplasia.** Hyatt Gainey Ranch Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 9-11—**Second Annual Spine Workshop.** Camelback Inn, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix 85013.

November 18—**Gynecologic Surgery.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Mon. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

December 14—**Genetics Update.** Flagstaff Medical Center, Flagstaff. Thurs. Contact: H. Eugene Hoyme, MD, (602) 795-5675 (Tucson) or William Austin, MD, (602) 774-1811 (Flagstaff).

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 21-22—**Modern Approaches to Allergy and Clinical Immunology.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. 15 hrs. $300. Contact: UCSF.

September 23—**Advances in Allergy and Infectious Diseases.** Alexian Brothers Hospital at Red Lion Inn, San Jose. Sat. 8 hrs. $25. Contact: Alexian Brothers Hospital, 225 N Jackson Ave, San Jose 95116. (408) 259-5000.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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Tables and Figures

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

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References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories

First Episodes (primary and nonprimary infections – commonly known as initial genital herpes).

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy, the severity of subsequent episodes and the effect on the natural history of the disease are still under study

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation

WARNINGS: Zovirax Capsules are intended for oral ingestion only

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY – Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative in another transformation system considered less sensitive

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.) At 50 mg/kg/day s.c in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day No effect upon implantation efficiency was observed when the same dose was administered intravenously In a rat peri- and postnatal study at 50 mg/kg/day s c there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day, s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v for one month

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day s c and i.v.) or in standard tests in the rat (50 mg/kg/day s c) In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat The clinical relevance of these findings is uncertain There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS – Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13 1%), diarrhea in 22 of 251 (8 8%), nausea and/or vomiting in 20 of 251 (8 0%), vertigo in 9 of 251 (3 6%), and arthralgia in 9 of 251 (3 6%) Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses) included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1)

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules) Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤ 10 ml/min/ 1 73 m^2

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200" – Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56)

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

US Patent No 4199574

* In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients

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CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

- **A remarkable safety profile**[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- **Protection against angina attacks**[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- **A decrease in myocardial oxygen demand**
  Resulting from a lowered heart rate-blood pressure product.[5]
- **Compatible with other antianginals**[6†]
- **Safe in angina with coexisting hypertension, COPD, asthma, or PVD**[1,3,5,6]

60 mg GREATER DOSAGE FLEXIBILITY 90 mg/120 mg

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

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CARDIZEM® diltiazem HCl/Marion

ANTIANGINAL PROTECTION PLUS SAFETY

Rx

Cardizem® (diltiazem HCl)

☐ 60 mg ☐ 90 mg

☐ 120 mg

Sig: tid

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%).

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing

References: 1. Schroeder JS. Mod Med 19B2;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA. Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frahlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 131)

ANESTHESIOLOGY

August 13-18—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $100. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 22-24—**Anesthesia Practice 1989.** Anesthesiology Educational Foundation at Hyatt Regency, Monterey. Fri-Sun. 12.5 hrs. Contact: AEF, PO Box 24230, Los Angeles 90024. (213) 825-0736.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. 15 hrs. Contact: UCD.

January 14-19—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

September 20—**Optimum Use of Diagnostic and Therapeutic Technologies in Clinical Practice.** American Heart Association Los Angeles at Beverly Hilton. Wed. 9 hrs. $120. Contact: Marlin Ledbetter, 3550 Wilshire Blvd, Ste 500, Los Angeles 90010. (213) 385-4231.

January 10-12—**Cardiovascular Disease in the Elderly.** UCI at Fess Parker's Red Lion Resort, Santa Barbara. Wed-Fri. Contact: UCI.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

DERMATOLOGY

October 14-15—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. 10 hrs. Contact: UCSF.

November 2-5—**International Hot Spots in Dermatology: The Patient, the Disease, the Physician and the Art.** Kauai Academy of Continuing Education at Stouffer's Waiohai Beach Resort, Poipu, Hawaii. Thurs-Sun. Contact: David J. Elpern, MD, PO Box 457, Kalaheo, HI 96741.

EMERGENCY MEDICINE

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. Contact: UCD.

December 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. $450. Contact: UCSD.

December 7-9—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 16 hrs. $220. Contact: UCSF.

INTERNAL MEDICINE

August 20-25—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $435. Contact: UCD.

September 4-5—**International Conference on Thyroid Metabolism.** UCI at Queen Mary Hotel, Long Beach. Mon-Tues. Contact: UCI.

September 7-9—**New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, PO Box 210211, San Diego 92121. (619) 453-6222.

(Continued on Page 138)

Most patients need only one.

K-DUR™ 20 Microburst Release System™
(potassium chloride) 20mEq Sustained Release Tablets

A daily prophylactic dose in a single tablet.

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K-DUR™ Microburst Release System®
(potassium chloride) Sustained Release Tablets

INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 137)

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. 16 hrs. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

OB/GYN

October 12-13—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott Hotel, Newport Beach. Thurs-Fri. Contact: UCI.

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

January 28-February 1—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

OPHTHALMOLOGY

August 25-27—**Regional Update Course in Ophthalmology: Section 1 of 3.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, Jules Stein Institute. (213) 825-9508.

September 15-16—**Uveitis Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Quail Lodge, Carmel Valley. Fri-Sat. Contact: UCSF.

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

PEDIATRICS

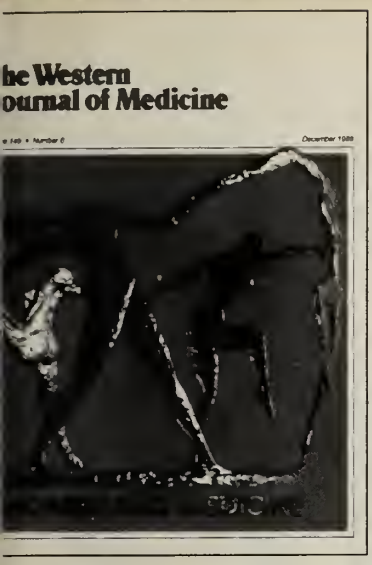
October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 3-5—**Current Advances in Pediatrics.** American Academy of Pediatrics California Chapter 4 at Disneyland Emerald Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: California Chapter 4, AAP, PO Box 1297, Orange 92668. (714) 978-2415.

November 4—**Pediatric Protein Metabolism.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

(Continued on Page 143)



Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

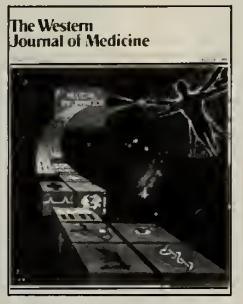
Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

IDS— Global rspective

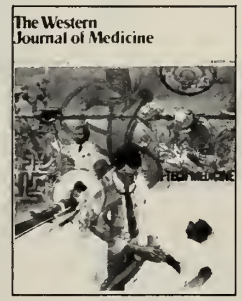
his issue, from the World Health anization, con- rs the methods limitations of S case reporting HIV serologic lies, summarizes les of transmis- , defines geo- hic patterns of ad, and examines epidemiology of infections by con- nt. Jonathan M. n, MD, Special e Editor, 1987.

Medical Informatics



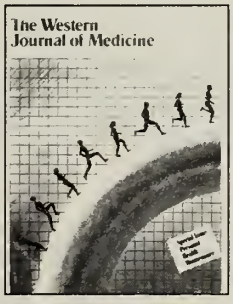
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



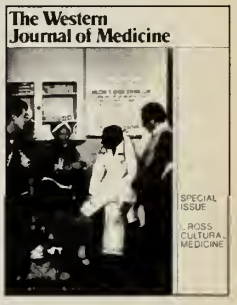
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*; ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia. Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.2% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema.* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension — Patients on Diuretic Therapy.* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release.* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents.* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium.* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium:* See WARNINGS, *Hydrochlorothiazide*, and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies of VASERETIC in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Enalapril Maleate: Post-marketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome: Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity, such as patent ductus arteriosus, have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects.* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk; however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Other adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Body as a Whole.* Syncope, chest pain, abdominal pain. *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia. *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Skin:* Pruritus, rash. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, decreased libido, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation; hypotension, angina pectoris. *Digestive:* Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, glossitis. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion, ataxia. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, pneumonia, bronchitis, rhinorrhea, asthma, upper respiratory infection. *Skin:* Herpes zoster, alopecia, flushing, photosensitivity. *Other:* Vasculitis, blurred vision, taste alteration. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide — Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 3418—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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(Continued from Page 138)

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 12-13—**North American Society for Pediatric and Adolescent Gynecology** at Red Lion Hotel, Costa Mesa. Fri-Sat. Contact: UCI.

January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

PSYCHIATRY

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

October 26-29—**Psychosomatic Medicine and Consultation-Liaison Psychiatry in a High-Technology World.** Academy of Psychosomatic Medicine at Riviera Hotel, Las Vegas, Nevada. Thurs-Sun. Contact: Academy of Psychosomatic Medicine, 5824 N Magnolia, Chicago, IL 60660. (312) 784-2025.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

RADIOLOGY

August 24-27—**Physics and Biology of Radiology.** UCSD at Town & Country Hotel, San Diego. Thurs-Sun. 25 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 7-10—**5th Annual Sonography Update for Physicians and Sonographers.** UCSD at San Diego Marriott Hotel and Marina. Thurs-Sun. 18 hrs. $275. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 23-24—**Weekend MRI Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Sat-Sun. 12 hrs. $195. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

October 2-5—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center and University of Cincinnati College of Medicine at Ritz-Carlton Hotel, Laguna Niguel. Mon-Thurs. 18 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 7-8—**Ultrasound Update: 1989.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. Contact: UCD.

October 12-14—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center Cincinnati at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sat. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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(Continued from Page 143)

December 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

SURGERY

August-December—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

August 21-25—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

September 15—**Ultrasonic Liver Surgery.** UCD at Davis. Fri. 8 hrs. $250. Contact: UCD.

September 22-24—**Frontiers in Solid Organ Transplantation.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sun. $125. Contact: UCLA.

October 11-14—**Hip and Knee Reconstructive Surgery 1989.** UCLA at Sheraton Kauai Hotel Poipu Beach, Kauai, Hawaii. Wed-Sat. Contact: UCLA. (213) 825-5840.

November 13-15—**21st Annual Surgical Congress.** Orange County Surgical Society at Le Meridien Hotel, Newport Beach. Mon-Wed. 16 hrs. Contact: OCSS, PO Box 1297, Orange 92666. (714) 978-3983.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

August 25-27—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 19 hrs. $235. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

September 8-9—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Napa. Fri-Sat. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

September 13-15—**Primary Care Medicine: Principles and Practice.** UCSF at The Portman, San Francisco. Wed-Fri. 20 hrs. $385. Contact: UCSF.

September 23—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Scripps Amphitheater. Sat. 6 hrs. $50. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

October 9-13—**Selected Topics in Sports Medicine in Conjunction With the Ironman Triathlon World Championship.** Tropical Seminars at Kona Surf Resort, Kailua-Kona, Hawaii. Contact: Robert Bethel, DO, PO Box 1399, Poulsbo, WA 98370. (206) 697-5776.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 21—**9th Annual Norman Sharrer Symposium: Common Difficult Treatment Syndromes.** Kaweah Delta District Hospital at Holiday Inn, Visalia. Sat. 6 hrs. $25. Contact: Kaweah Hospital, 400 W Mineral King Ave, Visalia 93291. (209) 625-7308.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 2-4—**The Challenge of Diabetes.** Annenberg Center for Health Sciences at Eisenhower at Rancho Mirage. Thurs-Sat. 15 hrs. Contact: Registration Secretary, (800) 321-3690.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas Hilton. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 2—**7th Annual Reider Laser Center International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers With ND: YAG Laser Workshop.** UCI at Center for Health Education, Long Beach. Contact: UCI.

December 6—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda at Los Angeles. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 891-2473.

December 9-10—**Travel Medicine '89.** American Society of Tropical Medicine and Hygiene at Honolulu, Hawaii. Sat-Sun. 12 hrs. $250. Contact: Linda Limauro, 20 York St, New Haven, CT 06504. (203) 785-2476.

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 12-13—**Clinical Nutrition.** UCD at Sacramento. Fri-Sat. Contact: UCD.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

IDAHO

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** University of Washington at Sun Valley. Fri-Sun. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 441-9762.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 146)

Millions of Americans are being asked to look out below

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Across the country, sexually active adults will soon be encouraged to do a special health check called a GSE... a genital self-examination. A simple examination to check for potential signs of a sexually transmitted disease (STD).

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*The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, and the American Osteopathic Association.

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(Continued from Page 144)

September 7-9—**Concepts and Controversies in Perinatal Care.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 9-10—**First American Cancer Society Interdisciplinary Cancer Conference.** Bishop's Lodge, Santa Fe. Contact: Stephanie Gooch, American Cancer Society, NM Chapter, 5800 Lomas NE, Albuquerque 87110. (505) 262-2336.

September 15-16—**Essentials of Health Care for the Elderly.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 15-16—**New Mexico Chapter, American College of Surgeons—Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: NM Chapter, ACS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

September 22-23—**Southwestern Psychiatric Symposium on Schizophrenia and Depression.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

October 12-14—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 21-23—**Utah Perinatal Association** (Sponsor: UUMC). Thurs-Sat. University Park Hotel, Salt Lake City. Contact: Raine Beach, (801) 581-2598.

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 7-9—**Annual Review of Neurology and Neurosurgery.** Seattle. Thurs-Sat. Contact: U/W.

September 8-10—**Issues in Obstetric Anesthesia.** Alderbrook Inn Resort. Fri-Sun. Contact: WSSA, (206) 441-6020.

September 11-15—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 15-16—**Allergy Update.** Seattle. Fri-Sat. Contact: U/W.

September 15-16—**Urology Update.** Seattle. Fri-Sat. Contact: VMMC.

September 16—**AIDS Issues.** Seattle. Sat. Contact: Evergreen Hospital, (206) 823-7599.

September 20—**AIDS Conference.** Everett. Wed. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 23—**AIDS Training for Washington State Professionals.** Seattle. Sat. Contact: WEAPA, (206) 448-4326.

September 29—**Neurology Update.** Tacoma. Fri. Contact: CME Pierce County.

September 29—**Ophthalmology Scientific Session—WSMA Annual Meeting.** Seattle. Fri. Contact: WSMA.

October 6—**Cardiology Conference.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 6—**23rd Annual Cancer Conference: Innovative Management of Cancer Patients.** Seattle. Fri. Contact: VMMC.

October 11-12—**Common Office Problems.** Tacoma. Wed-Thurs. Contact: CME Pierce County.

October 12-14—**Internal Medicine Review.** Seattle. Thurs-Sat. Contact: U/W.

October 19-21—**Washington State Academy of Physician Assistants Annual Fall Meeting.** Seattle. Thurs-Sat. Contact: VMMC.

October 27-28—**Sinus Surgery.** Seattle. Fri-Sat. Contact: U/W.

October 27-28—**Acid-Peptic Disease: New Perspectives.** Seattle. Fri-Sat. Contact: VMMC.

November 3—**The Injured Knee: Diagnosis, Treatment, and Therapy.** Seattle. Fri. Contact: VMMC.

November 3-4—**Medical Updates—School of Medicine.** Seattle. Fri-Sat. Contact: U/W.

November 10—**Sexual Abuse in Medical Practice.** Location to be announced. Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

November 10—**Outpatient Treatment of Infections: Oral Antibiotic Therapy.** Seattle. Fri. Contact: VMMC.

November 16-17—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 29-December 1—**Update on Surgery.** Seattle. Wed-Fri. Contact: U/W.

December 1—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 2—**AIDS Issues.** Seattle. Sat. Contact: Evergreen Hospital, (206) 823-7599.

December 6-10—**5th Annual Infectious Disease Conference.** Seattle. Wed-Sun. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 7-8—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** Sun Valley. Fri-Sun. Contact: U/W.

December 9-10—**The Anesthesiologists' Environment.** Seattle. Sat-Sun. Contact: WSSA, (206) 441-6020.

WYOMING

October 6—**Update on Infectious Diseases.** West Park Hospital, Cody. Fri. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody 82414. (307) 527-7501, ext 250.

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526. ◆

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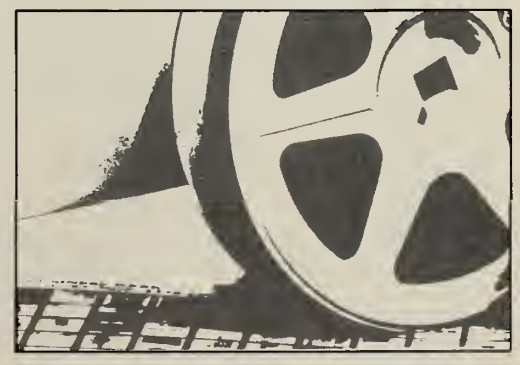

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Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia. Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions*.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients.

Angioedema. Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension. Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Vasculitis, muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings.

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions*.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d., and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS18R2(817)

MSD
MERCK SHARP & DOHME

In Memoriam

California Medical Association

GARNETT, W. GORDON. Died Mar 31, 1989, aged 82. Graduate of University of Kansas School of Medicine, Lawrence, 1933. Licensed in California in 1934. Dr Garnett was a member of the Los Angeles County Medical Association.

❧

GETZEN, LINDSAY C., Sacramento and Davis. Died May 1, 1989, aged 65. Graduate of Bowman Gray School of Medicine, Winston-Salem, North Carolina, 1953. Dr Getzen was a member of the Yolo County Medical Society.

❧

GORTON, JULIUS C., San Diego. Died Apr 4, 1989, aged 59. Graduate of California College of Medicine, Irvine, 1956. Dr Gorton was a member of the San Diego County Medical Society.

❧

HALL, SAMUEL PIKE, Oakland. Died Mar 5, 1989, aged 73. Graduate of Stanford University, 1941. Dr Hall was a member of the Alameda-Contra Costa Medical Association.

❧

HANSEN, ROBERT J. Died Jan 15, 1989, aged 69. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Hansen was a member of the Los Angeles County Medical Association.

❧

HEIGES, LAURENCE, JR, Lompoc. Died Mar 1989, aged 82. Graduate of Stanford University, 1933. Licensed in California in 1933. Dr Heiges was a member of the Santa Barbara County Medical Society.

❧

HOLM, ARVID D., Westminster. Died Mar 25, 1989, aged 77. Graduate of Northwestern University, Chicago, 1938. Dr Holm was a member of the Orange County Medical Association.

❧

HOOPER, WORTH A., Upland. Died Apr 23, 1989, aged 64. Graduate of University of Minnesota, Minneapolis, 1952. Licensed in California in 1953. Dr Hooper was a member of the San Bernardino County Medical Society.

❧

JELINEK, JOSEPH J. Died Mar 8, 1989, aged 93. Graduate of Rush Medical School, Chicago, 1921. Licensed in California in 1922. Dr Jelinek was a member of the Los Angeles County Medical Association.

❧

KANDELIN, ALBERT W. Died Feb 21, 1989, aged 77. Graduate of University of Michigan, Ann Arbor, 1940. Licensed in California in 1942. Dr Kandelin was a member of the Los Angeles County Medical Association.

❧

KEDDIE, FRANCIS M., Los Angeles. Died Apr 1, 1989, aged 82. Graduate of University of California, San Francisco, 1938. Licensed in California in 1938. Dr Keddie was a member of the Los Angeles County Medical Association.

❧

KOURI, PHILLIP, Anaheim. Died Apr 8, 1989, aged 66. Graduate of University of Oklahoma, Oklahoma City, 1947. Dr Kouri was a member of the Orange County Medical Association.

❧

MATHER, RALPH W. Died Mar 28, 1989, aged 81. Graduate of Harvard Medical School, Boston, 1933. Dr Mather was a member of the Los Angeles County Medical Association.

MATTAR, GEORGE E. Died Mar 31, 1989, aged 53. Graduate of National University of Ireland, 1958. Licensed in California in 1961. Dr Mattar was a member of the Los Angeles County Medical Association.

❧

MEAD, WILLIAM W. Died Jan 7, 1989, aged 75. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1937. Licensed in California in 1946. Dr Mead was a member of the Riverside County Medical Association.

❧

MENKE, JOHN F., Sacramento. Died Feb 3, 1989, aged 78. Graduate of Johns Hopkins University, Baltimore, 1938. Licensed in California in 1946. Dr Menke was a member of the Sacramento-El Dorado Medical Society.

❧

MITCHELL, CHARLES S., Fresno. Died Apr 20, 1989, aged 83. Graduate of University of California, 1932. Dr Mitchell was a member of the Fresno-Madera Medical Society.

❧

MOTLEY, HURLEY L. Died Mar 31, 1989, aged 84. Graduate of Harvard University, Boston, 1936. Licensed in California in 1947. Dr Motley was a member of the Los Angeles County Medical Association.

❧

MUNSON, RALPH E. Died Mar 8, 1989, aged 69. Graduate of Loma Linda University School of Medicine, 1948. Licensed in California in 1948. Dr Munson was a member of the San Mateo County Medical Society.

❧

NICKEL, WALTER R., San Diego. Died Apr 16, 1989, aged 81. Graduate of University of Minnesota, Minneapolis, 1938. Dr Nickel was a member of the San Diego County Medical Society.

❧

POLSE, MAX, San Francisco. Died Apr 12, 1989, aged 89. Graduate of University of Illinois School of Medicine, Chicago, 1927. Dr Polse was a member of the San Francisco Medical Society.

❧

SIMNER, ROBERT ROY, San Jose. Died May 16, 1989, aged 68. Graduate of Chicago Medical School, 1947. Dr Simner was a member of the Santa Clara County Medical Society.

❧

SLAGH, EDWARD P., Oakland. Died Feb 24, 1989, aged 67. Graduate of University of California, San Francisco, 1950. Dr Slagh was a member of the Alameda-Contra Costa Medical Association.

❧

SUMMERS, LLOYD F. Died Jan 18, 1989, aged 74. Graduate of University of Oregon, Portland, 1941. Licensed in California in 1947. Dr Summers was a member of the Los Angeles County Medical Association.

❧

TAYLOR, CARL J., Barstow. Died Apr 25, 1989, aged 71. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1952; California College of Medicine, 1962. Licensed in California in 1952. Dr Taylor was a member of the San Bernardino County Medical Society.

New Mexico Medical Society

GONZALES, SAUTURHINO M., Santa Fe. Died May 27, 1989, aged 89. Graduate of Tulane Medical School, New Orleans, 1936. Licensed in New Mexico in 1937. Dr Gonzales was a member of the Santa Fe County Medical Society.

TAGAMET® (brand of cimetidine)

See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg./5 mL., in 8 fl. oz. (237 mL.) amber glass bottles and in single-dose units (300 mg./5 mL.), in packages of 10 (intended for institutional use only).*

Injection:

Vials: *300 mg./2 mL. in single-dose vials, in packages of 10 and 30, and in 8 mL. multiple-dose vials, in packages of 10 and 25.*

Prefilled Syringes: *300 mg./2 mL. in single-dose prefilled disposable syringes.*

Single-Dose Premixed Plastic Containers: *300 mg. in 50 mL. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage®* Vials: *300 mg./2 mL. in single-dose ADD-Vantage® Vials, in packages of 25.*

'Tagamet' HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Baxter Healthcare Corporation, Deerfield, IL 60015.

**ADD-Vantage® is a trademark of Abbott Laboratories.*

BRS-TG:L7BB *Date of issuance Aug. 1988*

SK&F LAB CO., *Cidra, P.R. 00639*

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3:15 AM

Another night undisturbed by ulcer pain

The Promise... 'Tagamet' helps ulcer patients feel better fast.

The Proof... 80% of patients with duodenal ulcer, and 77% with gastric ulcer...even smokers, get pain relief with their first dose of 'Tagamet' 800 mg. h.s. That's effectiveness. That's fast relief.

For fast relief, rapid healing, effective prevention of duodenal ulcer recurrence, the longest record of safety and unmatched value, there's nothing like...

Tagamet®
brand of cimetidine
First to Heal™

First available, First in experience...First to Heal™

SK&F LAB CO.
Cidra, P.R. 00639
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Before prescribing, please see brief summary of prescribing information on adjacent page

rnal of the Arizona Medical Association

ARIZONA MEDICINE

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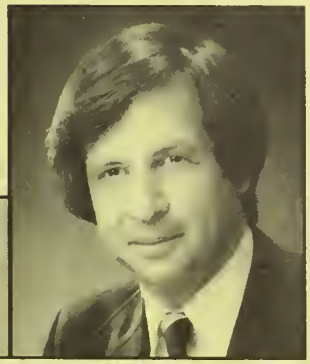
Patient Responsibility: Where Does It Begin and Where Does It End?



Marshall B. Block, M.D.

ife is a circle. The beginning and end are usually interchangeable. We come from the womb not g made any sounds for nine months to scream loudly at birth. We leave the way we came, noisily but ultimately lence. One of my father's more en- ening digressions during one of our e conversations dealt with this topic. ing in a retirement community has ntages and disadvantages. One of the depressing aspects is the slow but inual turnover of inhabitants as their ical conditions deteriorate and they r move on to facilities with greater rvised care or even worse. My father depressed by the fact that people he known for such a long time abruptly the community and were not seen or d from again. He then went on to say, y don't even say goodbye!" It was as felt they had a responsibility to say dbye to him before they left. It never urred to him that many either could not or had expired!

a similar vein, an increasing problem eveloping regarding patient/physician onsibility. This is an area of grave con- , especially in medical/legal matters, keeps recurring in different cir- stances, in different guises. For in- ce, a patient sees a physician and has blood tests obtained. The results return abnormal and even though the patient was instructed to return in one week he fails to keep his return appointment. The results are, thus, not transmitted to the patient. Should it be the physician's responsibility to contact the patient even though the patient and physician agreed that it would be the patient's responsibility to return to obtain the blood results? Most of us would say that it is still the physician's responsibility to contact the patient even though the patient has not consummated his portion of the agreement. Yet, what constitutes contacting the patient? Are one or two phone calls sufficient? Should one send a note asking the patient to return? How should the note be sent—certified, return receipt requested? If a physician sees a patient and tells the patient to see a neurologist because of headaches, but the patient fails to make the appointment and subsequently is found to have a serious brain problem, is the physician liable for not having more forcibly directed the patient to appropriate care earlier? When you refer a patient to another physician what are your responsibilities? Must you make the appointment for the patient or is giving the patient the physician's name and phone number sufficient? Is one name enough or should you give more than one name to a patient? If a patient is from an area in which you do not know competent specialists, should you suggest to the patient that he use his own skills to obtain a specialist? Would you be in more jeopardy if you referred the patient to a specialist whose practice was not up to snuff? Are you partly responsible for the results of the specialist if they are not good?

When does patient responsibility begin and physician responsibility end? The answers to these questions are sometimes difficult to ascertain. It appears that physician responsibility is finite, as patients do have the freedom to make their own choices based upon our suggestions. Intent is probably most important, especially if it is well documented.

MICA is faced continually with what appears to be good intentions on the part of physicians but no written records support their statements.

My father's expectations may have been unrealistic but patients perceive our responsibility to them in a similar vein and we must do our best to protect everyone's best interests. ■

Marshall B. Block, M.D.
Editor

Journal of the Arizona Medical Association

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In This Issue:

- Predicting Toxicity
- Lyme Disease
- New Helipad
- Child Drownings
- AIDS Report, Governor's Task Force
- Nursing: A Profession in Change
- Classified Ads

From Our President

Mark Ivey, Jr., M.D.

Recently the Arizona Hospital Association asked me to write an article for them about my thoughts on the delivery of health care in the 1990s and what role I thought physicians would have in that delivery.

It is rare that a country doctor from the hills of Arizona has an opportunity to address issues to hospital administrators, governmental policymakers, nurses, third party payors and private enterprise. When asked to do just that, I was reminded of my wife's uncanny ability to know what I did when I swore I wouldn't. I'm not clairvoyant, but I did try to give my views on those two questions, and I'd like to tell you what I said.

Physicians are very tired, angry, frustrated and fed up with non-physicians determining who does what to whom, when, for how long and at what price. This dollar-driven health care delivery system has left out the most important determinant of quality, and it has substituted quantity of care as the crucial factor in the health care formula.

The forgotten factor is the physician. But that's going to change. Medical staffs, associations and other groups of physicians will stand together to demand accountability for past wrongs and future decisions. The age of the passive medical staff and token board positions is over.

A combination of soaring liability insurance premiums and out-of-control jury verdicts coupled with exorbitant legal fees has been the catalyst for organizing these underdogs. We will buy hospitals, infiltrate boards, expose incompetence and demand excellence for our patients.

I see further crunching of the health care dollar that will coerce hospitals and physicians into marriages that, at times, will end in divorce. Turf battles will of necessity become major wars unless communication between the forces is reestablished with mutual respect.

I believe a progressively increasing share of the health care market will be paid for by the government, and there is a distinct possibility that a federally-mandated private insurance policy, means tested, will be available to all. This might even lead to reduction in care provided by the VA, Indian Health Service, AHCCCS and Medicare. When the public actually finds out that their health care providers are being paid more the less they do, the public will be *rightfully* outraged.

The voting public will continue to push for health care as a right, but the politicians will attempt to *not* pay for it, while telling the public they agree with the premise. This will allow the politicians to shift the blame for soaring costs onto health care institutions and physicians. But remember: their closets are not empty, and politically active health care individuals can make a difference.

As physicians step forward and lead this revolution in health care delivery, they will find they have many allies: nurses, aides, orderlies, technicians, and some hospital administrators.

By putting the patient first and refusing to be part of any system that won't, physicians will become part of a health care delivery system that will excel in quality as its efficiency improves. The doubting Thomases will be exposed along with the exorbitant health care contracts and salaries.

From the battlefield it isn't easy to know how the war is going. But like my wife and her uncanny intuitiveness, we physicians don't just see smoke; we can feel the fire. ■

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Predicting Toxicity

Certain of our colleagues and animal rights advocates are of the opinion that toxicity of environmental contaminants, drugs and other chemicals may be predicted soley with the help of computer programs. The majority of scientists, however, are not quite as optimistic. They maintain that the accuracy of predicting the relative toxicity of a new compound via computer programs is a function of the amount of previous information stored in the program and/or the reliability of the rules of operation. When more extensive toxicity informaiton is available on similar compounds the accuracy of the prediction will improve. Entirely new compositions of matter are not likely to be represented by themselves and/or by related compounds in the data bank and in addition they may constitute exceptions to the rules of operation; prediction of the toxicity of such new chemicals will then tend to be less reliable. Prudent toxicologists must therefore rely on both *in vivo* and *in vitro* animal experimentation to evaluate the potential toxicity of new chemical compounds such as drugs, agricultural chemicals, food additives and cosmetics. The intact animal is still the best indicator of entirely new toxic principles and it is the best system to use for subtle toxicity or toxicity apparent only after chronic dosing. On the other hand *in vitro* systems have their place in determining cellular and molecular mechanisms of toxicity. These systems can be used in screening for toxicity in a series of compounds once the target (i.e. organs, cells, subcellular organelles or enzymes) is known. One would expect that those *in vitro* systems that mimic the *in vivo* situation best are the more reliable ones to use. The following series depicts with increasing numbers the degree of physiological relevance of the system and, with decreasing numbers, the decline of parameters interfering with the elucidation of mechanistic aspects of toxic action:

1. isolated purified target molecule
2. preparation of subsellular organelles from the target organ.
3. culture of cell type responsible for toxicity
4. tissue culture of target organ explants
5. perfused whole target organ
6. intact animal

The choice of the most suitable *in vitro* system depends on the questions asked. Cell (3) and organ (4) culture systems occupy a central position in this series and are suitable systems to explore mechanisms of toxicity while still retaining reasonable physiological relevancy. Both systems help considerably in conserving experimental animals and are potentially applicable to human tissue.While pure populations of isolated cells have been extensively explored, organ culture in which multi-cell type interactions, cell ankering and histoarchitecture are retained has not been extensively used in toxicology. Because of the higher physiological relevance this latter experimental system might be useful for *in vitro* prediction of toxicity in humans.

Precision-cut organ slices can be easily produced from laboratory animal and human tissue such as kidney, liver, lung, heart, brain, spleen, etc. These slices can be maintained in organ culture and their viability measured using both general biochemical and organ-specific physiological parameters. The rate and extent to which such viability parameters are compromised over time in culture are a measure of organ-specific toxicity. Comparison of *in vivo* and *in vitro* experiments within animal species using physiological pharmacokinetics modeling software programs will yield the necessary approaches for prediction of toxicity in people from data obtained with human tissues *in vitro* . Only after having collected much more information utilizing these *in vitro* techniques will we be able to approach relying on toxicities solely predicted by computer. ■

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1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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APS and DPS helicopters land in the daisy field which served as a helipad for emergency rescue aircraft prior to construction of the new pad.

Hazardous Landings Are History

Until recently, Air Evac medical rescue helicopters had to drop past 60-foot high electric power distribution lines to land in front of Young's Pleasant Valley Community Medical Center. At night, or in high winds, or especially in both, such landings were almost as perilous as the patients' conditions that called for air rescue in the first place.

Thanks to three years of fund raising and negotiations, and a lot of hard work by the community, the clinic at Young has a brand new helicopter landing pad in an open area away from the power lines. ArMA President Mark Ivey, Jr., M.D., credits the cooperation of Pleasant Valley Medical Board, clinic staff, women's auxiliary, residents of the Young area, Department of Public Safety, APS and Samaritan Health Services.

Donations toward purchase of the acre of land immediately north of the clinic for the helipad—and for its construction—were given by individuals, APS and Samaritan; much of the funding was raised by the Women's Auxiliary Thrift Shop. Thrift shop proceeds also support the operation of the medical center, which is run by Intermediate Emergency Medical Technician Kathy Cline. Medical care is provided through Dr. Ivey's Pine Country Medical Center, which serves much the rural area between Pine, Strawberry, Young, Payson and the Mogollon Rim.

Samaritan's Air Evac hovers over the new helipad prior to becoming first to land and christen the structure.

Young Folks Celebrate New Helipad

The community turned out to celebrate the dedication of the Pleasant Valley Medical Center's first concrete helicopter pad, built and funded by volunteer contributions.

During dedication ceremonies, special presentations were made to ArMA President Mark Ivey, Jr., M.D., Kathy Cline, I.E.M.T., and Samaritan Health Services Regional Operations Group Vice President Luther Goehring, as well as to the members of the local community who were instrumental in the construction of the helipad.

Music for the occasion was provided by Dr. Ivey's country and western band; food was provided in quantity and high quality by the women's auxiliary; good fellowship was provided by all.

Samaritan Health Services sent an Air Evac helicopter to christen the helipad and demonstrate to the community its air rescue capacity. Also flying in for the occasion were representatives of the Department of Public Safety and Arizona Public Service Company.

IEMT Kathy Cline and Samaritan officials discuss first landing at the new Pleasant Valley Medical Center's helicopter pad.

The staff of Pine Country Medical Center, above, who provide medical care throughout Gila County from Roosevelt Lake to the Mogollon Rim, along with hundreds of Pleasant Valley area residents celebrated the dedication of Pleasant Valley Medical Center's new helicopter landing pad. Food, left, provided by the women's auxiliary, provided ample reason to line up, bottom picture. Music for the occasion was provided by Dr. Ivey's country/western band, below, and a good time was had by all.

Questions and Answers on Lyme Disease
(Reprinted Courtesy of the Centers for Disease Control)

Lyme Disease

Contrary to most national information, Lyme Disease is alive and flourishing in Arizona. According to Arizona's fledgling Lyme Disease Association, at least a dozen cases of the tick-transmitted multisystem inflammatory bacterial infection have been diagnosed. The following information is provided by the U.S. Centers for Disease Control.

1. What is Lyme disease?

Lyme disease is a bacterial infection caused by a spiral shaped microorganism called spirochete. The name of the Lyme disease bacterium is *Borrelia burgdorferi*, consequently the disease often is called lyme borreliosis.

2. How is Lyme disease spread?

Lyme disease is spread by the bites of certain ticks. The deer tick, *Ixodes dammini*, is responsible for transmitting the infection in the northeastern and central United States. On the Pacific Coast and in the southeast, Lyme disease is spread by black-legged ticks that closely resemble the deer tick.

3. How do ticks carrying Lyme disease differ from other ticks?

The most important distinction is size. The vector ticks of Lyme disease are much smaller than dog ticks and cattle ticks. The nymphal stages of *Ixodes dammini* which are chiefly responsible for transmitting infections to humans are black and no bigger than a pinhead. The adult tick, which may transmit infections in the fall, is only slightly larger.

4. What are the early symptoms of Lyme disease?

The earliest signs of Lyme disease are flu-like symptoms (fatigue, chills, fever, headache, muscle and joint pains) and a very characteristic skin rash called erythema migrans. This rash generally appears as a red circular patch that expands slowly, often to a very large size. The center of the patch may clear as the rash enlarges, resulting in a ring-like appearance. The rash may be warm but is not painful.

5. What are the later manifestations of Lyme disease?

Some of the symptoms of Lyme disease may not appear until weeks or months after the initial onset of illness. The infection may inflame the heart, leading to disturbances of the heart rhythm. Lyme disease may affect the nervous system causing muscle weakness of the face and limbs or pain and numbness. Meningitis, an inflammation of the covering of the brain, may occur, resulting in a stiff neck and severe headache. In later stages of the disease, arthritis may develop, and the joints may become red, swollen and painful.

6. How is Lyme disease diagnosed?

Lyme disease is diagnosed from its clinical features and with the aid of serological (blood) tests. Often the serologic test does not become positive until several weeks after the onset of illness.

7. Can Lyme disease be treated and cured?

Most Lyme disease patients treated in early stages of the disease, when only rash and flu-like symptoms are present, will respond favorably to therapy and remain well. Even among patients not treated until later stages of the disease, the majority respond to therapy. In a small proportion of cases, symptoms may recur and additional courses of antibiotics are necessary. Permanent damage to joints occurs in a small number of patients.

8. What antibiotics are used to treat Lyme disease?

Tetracyclines (tetracycline, doxycycline) and penicillins (penicillin, ampicillin) are usually used in treating early stages of Lyme disease. Intravenous penicillin and ceftriaxone are commonly used to treat patients in later stages of the disease. Other antibiotics and drug combinations are under evaluation.

9. Are there special problems if Lyme disease occurs during pregnancy?

Lyme disease acquired in pregnancy may lead to infection of the fetus. Although some cases of fetal infection resulting in malformations and miscarriage have been reported, there have been no reported instances of an adverse outcome when the expectant woman was adequately treated.

10. Where does Lyme disease occur?

Lyme disease occurs in a nearly worldwide distribution in Europe, Asia, Australia and North America. In the United States Lyme disease has been acquired in almost all states, including Arizona.

11. Is Lyme disease spreading?

Yes, the tick vector of Lyme disease is now present in areas of the country where it had not been recognized previously. The tick can be spread by birds, deer, and by humans transporting pets, including horses.

12. Where am I likely to be exposed to ticks carrying Lyme disease?

The tick vectors prefer wooded areas and overgrown fields. However in many suburban areas where residential lawns and parks are located within or near woods, ticks may be found in the grass. Local health departments, park or extension services may have information on the local distribution of ticks.

PRECAUTIONS

1. Avoid areas infested with *Ixodes dammini*.
2. Wear light colored clothing so that adherent ticks are visible.
3. Wear long pants and long sleeved shirts.
4. Use repellents on clothing and or skin. Follow label directions and avoid excessive use.
5. The longer an infected tick stays attached, the greater the likelihood it will transmit infection. Inspect yourself frequently. They are small and may be difficult to find. If you discover any, carefully remove immediately, preferably with tweezers. ■

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Claim forms are available from, and must be filed with, Robert D. Balzano, Receiver, Empire Casualty Company, 333 W. Colfax Avenue, Suite 515, Denver, Colorado, 80204.

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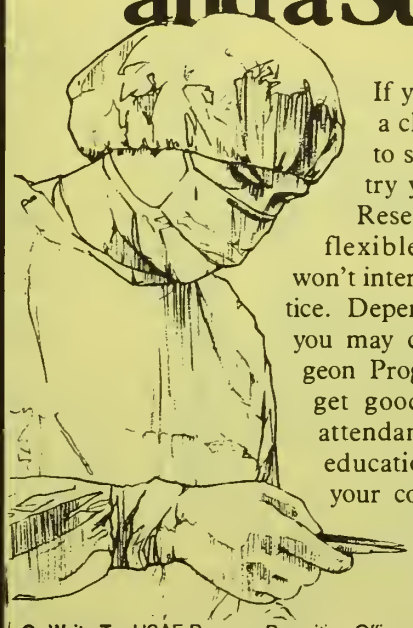

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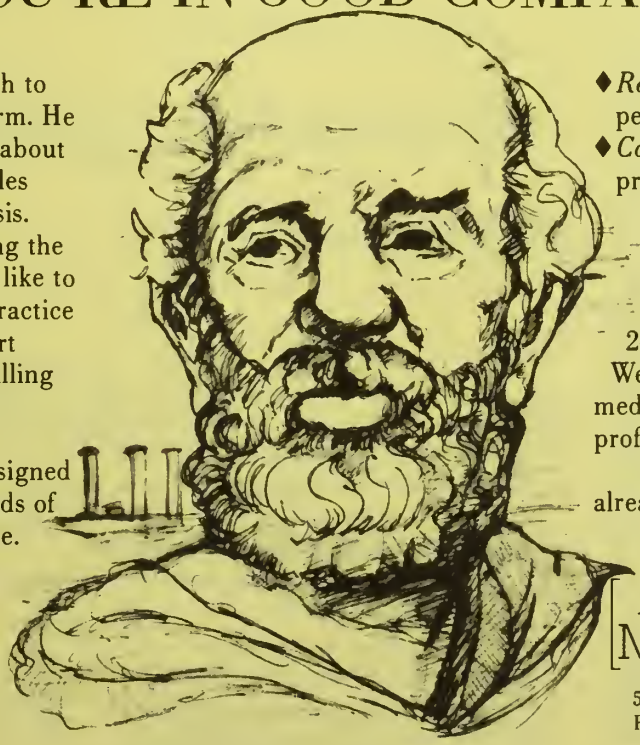

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Physicians Can Help Prevent Child Drownings

By Timothy Flood, M.D., Arizona Department of Health Services

Drowning of young Arizona children is receiving more attention this year than in past years. The attention is well deserved. Drowning leads all causes of death for 1 - 4-year-olds, surpassing even motor vehicle deaths and deaths from illness. Since 1981 approximately 30 Arizona children under five years of age have drowned each year (figure 1). Most drownings of children age 1 - 4 occur in backyard pools; an average of three infants die each year in tubs and toilets. Arizona's drowning rate of children is three times the national rate (figure 2). In excess of two-hundred 9-1-1 calls are made each year for near drowning incidents; many survivors of near drowning incidents are left neurologically impaired.

The 1989 statistics show no decrease in the number of incidents and deaths compared to previous years. During the first six months of 1989 more than eighty-eight 9-1-1 calls have been handled by the Phoenix and Tucson metro area fire departments. Seventeen persons have died, including fifteen children under the age of five. These statistics are disturbing in light of past and present efforts to educate the community about the hazards of drowning.

Physicians and other health professionals can help in the education of parents, grandparents, and other adults who supervise children. Patient education materials including literature, pamphlets, and video cassettes are available from a number of sources. These materials stress the importance of multiple barriers to the pool, starting with knowing where young children are at all times. Physicians can discuss the relative importance of other interventions: adequate fences and self-latching gates, training of baby sitters, knowing CPR, whom to call in an emergency, swim lessons, etc. Materials are available from most fire departments in the Phoenix and Tucson area; from the Tucson Drowning Prevention Committee (881-0107); from community relations offices at Phoenix Childrens' Hospital, St. Joseph's Hospital (Phoenix), and Tucson Medical Center; and from local health departments.

Current efforts continue to be targeted at increasing parental and adult supervision. The Maricopa County Drowning Prevention Coalition has brought together a diverse group, which includes fire departments, hospitals, health departments, media and public relation experts, pool builders, parents and others interested in drowning prevention. Educational campaigns and fairs have distributed a number of messages including "Children Aren't Waterproof," "Watch your Kids Around Water," and now the Phoenix Fire Department warning that "Just a Few Seconds" is all it takes for a child to drown in a pool. Similar efforts in Pima county through the Tucson Drowning Prevention Committee also have been active in educating the public and professionals. ■

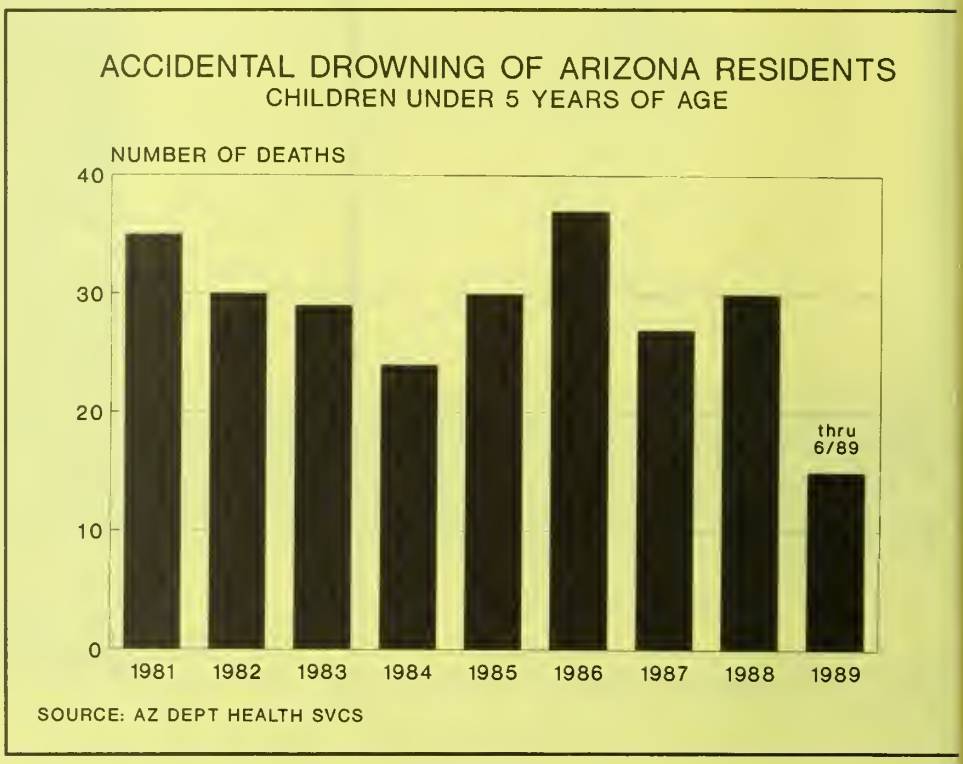

FIGURE 1

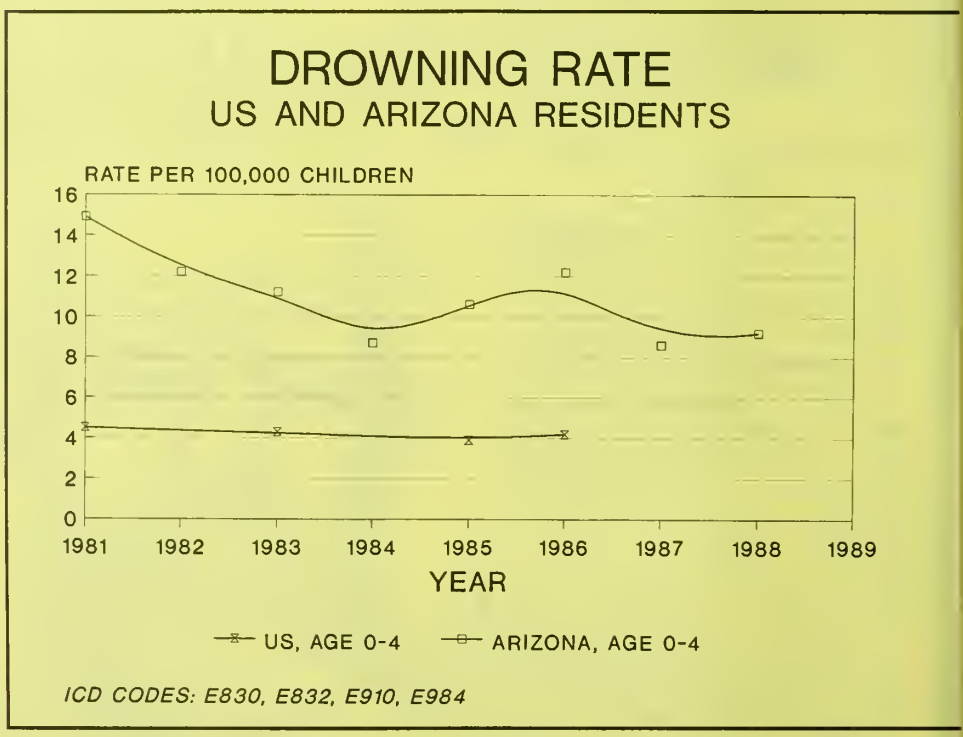

FIGURE 2

Nursing: A Profession In Change

Hospitals nationwide are facing a shortage of their most essential personnel - nurses. According to a December 1988 survey by the Arizona Hospital Association, the average vacancy rate for registered nurses in the state's hospitals is 10 percent and 11 percent for licensed practical nurses.

Hospitals, which employ 68 percent of all registered nurses, have endured such shortages in the past. Vacancies over the past three decades led to the development of new roles for nurses and other health care professionals, including the creation of "technical" nurses who require only two years of training. Ancillary health care professionals - respiratory therapists, medical technologists and physician assistants - also grew out of these shortages.

"This nursing shortage is different from those of the past," said John Rivers, president of the Arizona Hospital Association. "While vacancies in hospitals continue to rise, enrollments in nursing schools are down."

The current nursing shortage is more complex than those of the past. Social and economic factors as well as the changing health care system have all impacted the shortage. The primary reason for the shortage, experts agree, is that the traditionally female-dominated nursing profession must now compete with many other career choices which previously had limited opportunities for women.

"The two most popular majors for women in college today are pre-med and accounting," said Katy Bond, RN, supervisor of Nurse Recruitment, St. Joseph's Hospital and Medical Center, Phoenix.

Nurses working in the field also have a variety of options. Their knowledge is in demand as product development consultants for industry, pharmaceutical and medical equipment sales representatives, and quality assurance specialists for insurance companies. Their skills may also be put to use in ambulatory care and outpatient surgery settings and as home health nurses.

The current nursing shortage also coincided with the introduction of Medicare's prospective pricing system (PPS) in 1984. This was followed closely by the introduction of health maintenance organizations (HMOs) and preferred provider organizations (PPOs) by the private sector. All of these programs encourage outpatient care whenever possible. If inpatient care is necessary, efficiency is strongly encouraged. As a result, hospitalized patients tend to be more severely ill than in the past and in greater need of nursing care.

While these demands on nurses have increased, their salaries have remained relatively steady. Although starting salaries for nurses are competitive with other professions, the ranges are narrow. The average annual salary is about $25,000 per year and the maximum is approximately $30,000 annually.

To deal with this, hospitals are beginning to develop "clinical ladders," or career paths for nurses. This should bring greater mobility within hospital nursing.

"We're looking closely at our preparatory tracks," said Rhonda Anderson, RN, senior administrator of Patient Care Services at Good Samaritan Medical Center. "We're offering educational programs for the nurse, for example, who has been in telemetry for five years and wants to move into critical care. Since nurses are so specialized today they need that preparation to move into other areas." ■

Report From The Governor's Task Force on AIDS

Jane Harris Aiken, J.D., M.L.

The Governor's Task Force on AIDS was created by executive order in September of 1988. Its 36 members include physicians, nurses, social workers, clergy, lawyers, community workers, people from the business community and representatives from all of the executive agencies and the Legislature. The Task Force has held over 50 meetings in which the group has heard from people living with HIV disease, people who provide care for HIV-infected people and concerned members of the public who come in contact with people with HIV infection. Other groups dealing with AIDS-related issues have shared information and ideas with our group as well. The Task Force issued its Interim Report on June 20, 1989. Obviously, because AIDS is primarily a medical problem, many of the issues raised by the Task Force may be of particular interest to Arizona physicians and health care professionals. The report outlined the broad ways that the State could respond to the epidemic. We are considering a multitude of ideas. I will highlight those that may be of particular interest to you. Suggestions from the medical community would be greatly appreciated.

Perhaps the most disturbing information that the Task Force has received came from the Greater Phoenix Affordable Health Care Foundation confirming information that Task Force members had heard from many people. Less than two percent of the physicians in Arizona are providing ongoing care for people with HIV disease. We have heard of patient dumping, of patients turned away from physicians' offices once their HIV-positive status was revealed, and of physicians unable to find other doctors willing to cover their HIV-infected patients during their time off. Several possible reasons have emerged for physicians' unwillingness to handle these cases. These include concern by the physician that he or she is not qualified to provide the necessary care for the HIV-infected person, concern that other patients will be frightened away if they see an HIV-infected person in their waiting room getting care, fear that since the disease may require experimental treatments that care will go unreimbursed and finally fear of contracting the disease through caring for the patient.

The Task Force is attempting to address all of these concerns on the part of physicians. We are considering strategies that include educating health professionals about HIV and ensuring appropriate infection control procedures, creating a standard of care review board to establish a baseline standard of care that can be used by physicians who are treating HIV-infected individuals and as a standard for insurance schemes to authorize reimbursement. The Task Force is also considering the feasibility of creating HIV clinics that would provide centers of excellence for treatment of people with HIV disease. St. Joseph's Hospital in Phoenix, in conjunction with the Task Force, has convened a meeting of physicians from all over the state to discuss these proposed strategies, assess the needs of physicians within the state, and start developing a baseline for care of HIV-infected individuals. The results of that meeting should move us forward in developing meaningful proposals for the State to implement.

Physicians are also faced with a very difficult dilemma in which there are two competing and legitimate needs: the need to ensure the confidentiality of HIV-infected individuals to prevent the discrimination and stigmatization associated with the disease and the medical needs of the patient and the need to prevent unnecessary spread of the disease. Moral choices should not be made by taking an assessment of liability exposure. The Task Force is studying the ways the law should handle the duty to warn. One of the possible legal solutions is to relieve a physician of liability for warning or failing to warn provided that the actions were not grossly negligent. This would leave the choice to the physician where it best resides.

Unfortunately since HIV disease is associated with socially stigmatizing behaviors, breaches in confidentiality can have devastating effects on the patient. The Task Force is looking at several ways to create added protection for confidentiality without hamstringing those health care professionals who have a need to know. These include procedures to make medical records more secure, requiring informed consent that is specific to HIV testing and requiring written authorization before the result of an HIV test is disclosed.

In the next several months the Task Force will be refining our ideas and making choices about what the State should do and what is better left to a public/private partnership. In order for the final report to have a firm grounding, the input of Arizona physicians and health care professionals is essential. We urge you to become involved. To get on our mailing list, please call Julie Marshall, the Task Force staff person, at 230-5818.

Biography

Jane H. Aiken is a Professor of Law at A.S.U. College of Law. She has a Juris Doctorate from New York University School of Law and a Masters of Law from Georgetown University Law Center. She has published several articles in the area of AIDS and the law including "AIDS and Civil Liberties," "AIDS and Education" and "Women and AIDS." Professor Aiken teaches Gender, Sexuality and the Law as one of her courses at A.S.U. Jane Aiken is Chair of the Governor's Task Force on AIDS. ■

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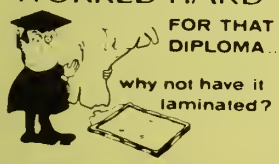

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Clinical Investigation

Diurnal Rhythms of Cortisol, ACTH, and β-Endorphin Levels in Neonates and Adults

K. WAYNE HINDMARSH, PhD; LEONARD TAN, MBBS, MPH, PhD; KORAVANGATTU SANKARAN, MD, FRCP(C); *and* VICTOR A. LAXDAL, PhD, FCAB, *Saskatoon, Saskatchewan*

To determine whether a diurnal rhythm exists in neonates admitted to neonatal intensive care units where there is continuous artificial lighting and periodic nursing and medical care, plasma cortisol, adrenocorticotropin (ACTH), and β-endorphin concentrations were measured in two groups of infants and in adult human volunteers. As expected, a diurnal rhythm was seen in adults. A diurnal rhythm was also found for cortisol and endorphin levels in neonates (3 to 4 days postnatally) with minimal stress and in infants who were clinically severely stressed. There was not a significant difference between the morning and afternoon concentrations of ACTH in these infants, but the afternoon concentrations were lower than the morning's, as would be expected. We found that a diurnal rhythm does exist in neonates within the first few days of postnatal life and that the continuous lighting and medical and nursing interventions do not interfere with this rhythm.

(Hindmarsh KW, Tan L, Sankaran K, et al: Diurnal rhythms of cortisol, ACTH, and β-endorphin levels in neonates and adults. West J Med 1989 Aug; 151:153-156)

The endogenous opiate, β-endorphin, is derived from proopiomelanocortin, the same precursor as for adrenocorticotropin (ACTH) and β-lipotropin.[1] Plasma concentrations of β-lipotropin and ACTH have been correlated with certain physiologic and clinical conditions and have shown a diurnal rhythm.[2,3] There is also evidence for a diurnal rhythmicity of β-endorphin and cortisol in human adults.[4,5]

In a number of clinical studies done in our laboratory, we have noticed an increase of plasma and cerebrospinal fluid β-endorphin concentrations during various pathophysiologic conditions.[6-9] During these studies the timing of blood collections was kept consistent because of the possibility of a diurnal rhythm. One report has suggested that a diurnal rhythm is a function of maturation and does not occur before 6 months of age.[10] Further, the infants in neonatal intensive care units are exposed to constant artificial light, and their sleep patterns are disrupted by periodic nursing and medical interventions.[11] Both of these factors may disrupt a biologic rhythm. Therefore, we measured the cortisol, ACTH, and β-endorphin concentrations from morning and afternoon blood specimens in three groups of human subjects to ascertain whether a diurnal rhythm existed in these infants.

Subjects and Methods

The study included 10 healthy adult volunteers and 20 neonates who were admitted to the neonatal intensive care unit of the University Hospital, Saskatoon, Saskatchewan, during a six-month period. The study was approved by the University of Saskatchewan Hospital Advisory Committee on Ethics in Human Experimentation, and informed parental consent was obtained before the study. The adult volunteers served as a control for the analytic techniques and previously proven diurnal rhythms.

The infants were divided into two groups according to the following criteria:

- Group 1 consisted of ten infants (5 male, 5 female) who were appropriate for their gestational ages. The gestational age ranged from 30 to 36 weeks (mean 33.4 ± 0.6 standard error of the mean) according to maternal dates and subsequently confirmed by gestational assessment. Postnatal ages were from 3 to 4 days (3.3 ± 0.2), and body weights were from 1,780 to 3,270 grams ($2,359 \pm 147.4$). The infants were breathing spontaneously and had a diagnosis of mild hyaline membrane disease or wet lung disease (or both). All infants in this group showed minimal or no stress clinically as described previously.[12]
- Group 2 consisted of ten infants (5 male, 5 female) who were appropriate for gestational ages—28 to 37 weeks (31.7 ± 1.1)—at postnatal ages 3 to 4 days (3.3 ± 0.2), and who had body weights of 1,040 to 3,190 grams ($1,846 \pm 250$). These infants suffered from severe hyaline membrane disease with or without apnea and were mechanically ventilated. They received intermittent chest physiotherapy and endotracheal suctioning and were considered clinically stressed.[11] Management of the infants was not altered for this study and was according to guidelines previously published.[13]

The adult volunteers (5 male and 5 female), making up group 3, ranged in age from 24 to 42 years (32.5 ± 1.7) and weighed between 52 and 78 kg (67.4 ± 2.6).

Blood specimens were collected by venipuncture or from

From the University of Saskatchewan College of Pharmacy (Dr Hindmarsh), the Department of Community Health and Epidemiology (Dr Tan), Perinatal Research Laboratory, Department of Pediatrics (Dr Sankaran), and the Department of Chemical Pathology (Dr Laxdal), University of Saskatchewan College of Medicine, Saskatoon, Saskatchewan.

This work was supported in part by an operating grant (MA-9174) from the Medical Research Council.

Reprint requests to K. Wayne Hindmarsh, PhD, College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada.

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropin
CRF = corticotropin-releasing factor

an indwelling arterial line into tubes containing ethylenediaminetetraacetic acid as an anticoagulant at 9:30 AM and 3:30 PM. The specimens were immediately placed on ice and transferred to the laboratory where they were centrifuged (1,000*g* for 10 minutes). The plasma was carefully separated and frozen at −70°C until used for β-endorphin, ACTH, and cortisol assays.

Analysis

β-Endorphin was isolated from plasma in a manner similar to that previously described[6,14] using a Sephadex G-50 (superfine) column (Pharmacia Fine Chemicals). Plasma β-endorphin concentrations were measured by a radioimmunoassay purchased from New England Nuclear.[6] Lyophilized specimens were reconstituted in 1 ml of buffer (0.1 mol per liter phosphate buffer, pH 6.0).[6] Plasma ACTH and cortisol concentrations were also determined by radioimmunoassay using kits purchased from Radioassay Systems Laboratories Inc (Carson, California) and Diagnostic Products Corporations (Los Angeles), respectively. The antiserum has low cross-reactivities to other naturally occurring steroids. Adrenocorticotropin sensitivity, as defined by variations from the zero standard, was (±2 standard deviations) 0.4 pmol per liter. Cortisol sensitivity was 5.5 to 1,380 nmol per liter. Commercially available control specimens for cortisol were also assayed along with the specimens in the study. The calculated concentration for these control specimens was within the stipulated range. Duplicate measurements were obtained for each specimen. The intra-assay and interassay variations were 4.1% and 8.8%, respectively, for cortisol and 6.0% and 10.7% for ACTH.

Data Analysis

The data were analyzed by nonparametric paired comparison using the Wilcoxon's signed rank test in which morning readings were paired with the afternoon readings of the same persons. A P value of less than .05 was considered significant. All values are given as the mean ± 1 SEM.

Results

No significant differences existed in gestational ages, postnatal ages, or body weight in the infants assigned to groups 1 and 2.

The mean plasma morning (and afternoon) concentrations for cortisol, ACTH, and β-endorphin in group 1 were 124.0 ± 20.0 (89.4 ± 11.2) ng per ml, 10.6 ± 1.4 (8.8 ± 0.8) pg per ml, and 25.3 ± 3.5 (19.0 ± 2.9) pg per ml, respectively. The distribution for the concentrations of all three substances is shown in Figure 1. There was a statistically significant difference between morning and afternoon cortisol and β-endorphin concentrations. A significant difference was not seen for ACTH levels between the two collection periods ($P = .08$), although the PM concentrations were lower. Group 2 (Figure 2) morning (afternoon) concentrations of cortisol, ACTH, and β-endorphin were 179.3 ± 32.5 (146.0 ± 28.1) ng per ml, 9.1 ± 1.1 (8.5 ± 1.2) pg per ml, and 46.0 ± 8.2 (22.4 ± 3.6) pg per ml, respectively. A statistically significant difference was found between the morning and afternoon concentrations of the cortisol and β-endorphin concentrations in this group. As in group 1, the ACTH concentrations for group 2 were lower in the PM but not significantly ($P = .07$). There were no observable differences in values between male and female infants in either group nor was any relationship seen between responses and gestational age.

In the adult volunteers (group 3, Figure 3) all three substances revealed, as expected, a statistically significant difference between morning and afternoon concentrations. A diurnal rhythm was thus observed. The mean concentrations detected were as follows: cortisol, 190.7 ± 23.4 (127.0 ± 19.7) ng per ml; ACTH, 10.4 ± 1.2 (9.2 ± 1.1) pg per ml; and β-endorphin, 23.8 ± 3.0 (16.5 ± 2.1) pg per ml.

Discussion

Various biologic rhythms have been shown in humans and animals.[2,4] When the cycle of changes in concentrations is of 24 hours' duration, it is referred to as a circadian rhythm. Although diurnal and circadian rhythms are sometimes used interchangeably, the former is restricted to the variations of concentrations in the daylight hours.[15] This study has thus concerned itself with the diurnal rhythm because measurements were made during the daytime hours, although a circadian rhythm has been shown for these hormones and β-endorphin in adults. Ideally, more frequent blood specimen collections covering the 24-hour cycle would have been better, particularly because of the episodic nature of the secretion and release of these hormones. We measured the concentrations from two specimens mostly because of the convenience of collecting specimens and because we did not want to compromise the infants.

The concentrations recorded for cortisol, ACTH, and β-endorphin in the adult group showed that the 9:30 AM and 3:30 PM sampling times were suitable for showing a plasma variation related to a known biologic rhythm. These findings agree with those of Dent and co-workers, who showed that the highest cortisol and immunoreactive β-endorphin levels occur between 4 and 10 AM.[4] A similar pattern was seen for cortisol and β-endorphin concentrations in both groups of neonates participating in this study (Figures 1 and 2). Adrenocorticotropin concentrations did not differ significantly between the two collection periods in either group of neonates. This could partially be explained by the small sample size, the episodic nature of ACTH release, and by maturational differences. Food ingestion may also influence the secretory pattern of ACTH.[4,16(p131)] The half-lives of hormones vary in newborns, and this variation may indeed be more significant in sick premature neonates. There are also reports that ACTH concentrations do not always parallel plasma cortisol concentrations.[4,17,18] Adrenocorticotropin and β-endorphin are under control of the corticotropin-releasing factor (CRF). A similar pattern would therefore be expected for the two substances.

A linkage between ACTH and β-endorphin circadian secretion and CRF release has been confirmed in human and animal studies.[12] The CRF circadian rhythmicity is regulated by serotoninergic and cholinergic pathways that in turn are characterized by a circadian periodicity in their hypothalamic concentrations. Infants in group 1, although minimally stressed, were still sick. In other words, they cannot be classified as ideal control neonates. This fact may also account for the absence of a significant difference between the AM and

PM levels of ACTH. The fact that the concentrations of cortisol and β-endorphin showed a diurnal rhythm may indicate that these hormones have a stronger influence on self-preservation than does ACTH.

It is interesting that a diurnal rhythm for cortisol and β-endorphin was seen in these young neonates who are only 3 or 4 days of age because earlier reports, which dealt with children aged 2 months to 3 years of age, suggest that a typical circadian adrenocortical rhythm does not exist at these ages.[19-21] The heterogeneity of the populations in the studies by Onishi and associates, Franks, and Beitins and colleagues could account for their results.[19-21]

A diurnal rhythm was evident in the infants of group 2 despite the fact they were ill and stressed. Cortisol and β-endorphin levels were higher than those seen in the minimally stressed neonates (group 1). An elevated release of β-endorphin in stressed neonates has been reported previously.[6-8]

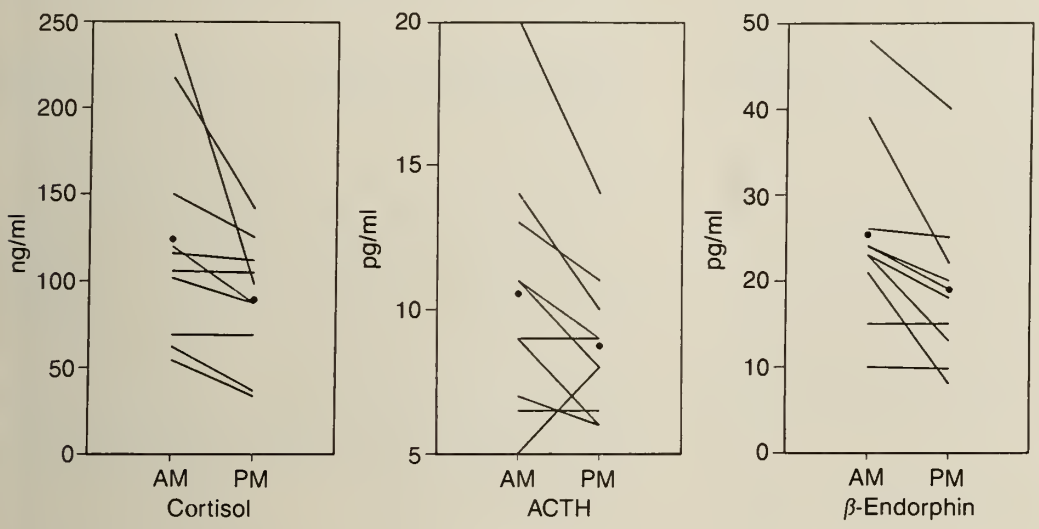

Figure 1.—Morning and afternoon concentrations of cortisol, adrenocorticotropin (ACTH), and β-endorphin are shown for 10 minimally stressed neonates. • = mean

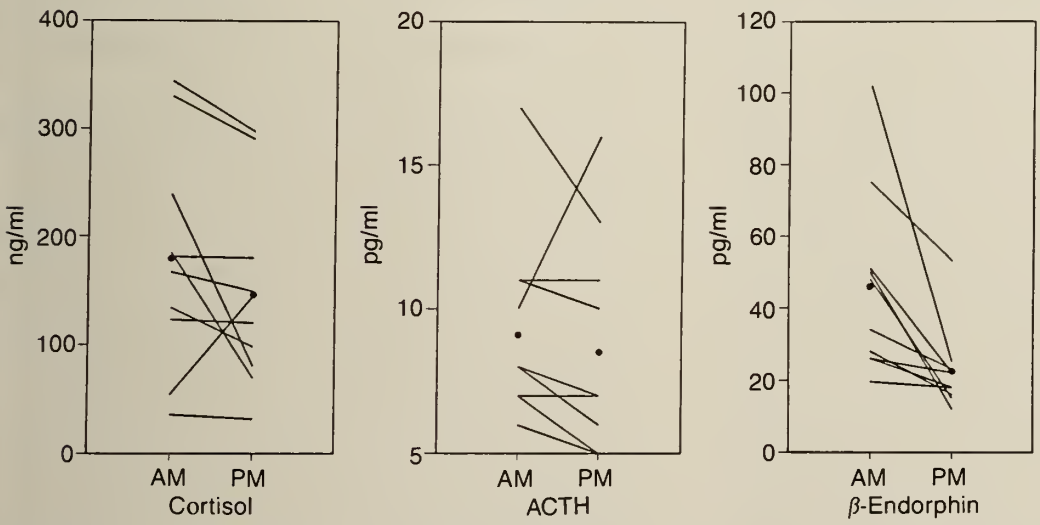

Figure 2.—Morning and afternoon concentrations of cortisol, adrenocorticotropin (ACTH), and β-endorphin are shown for 10 clinically stressed neonates. • = mean

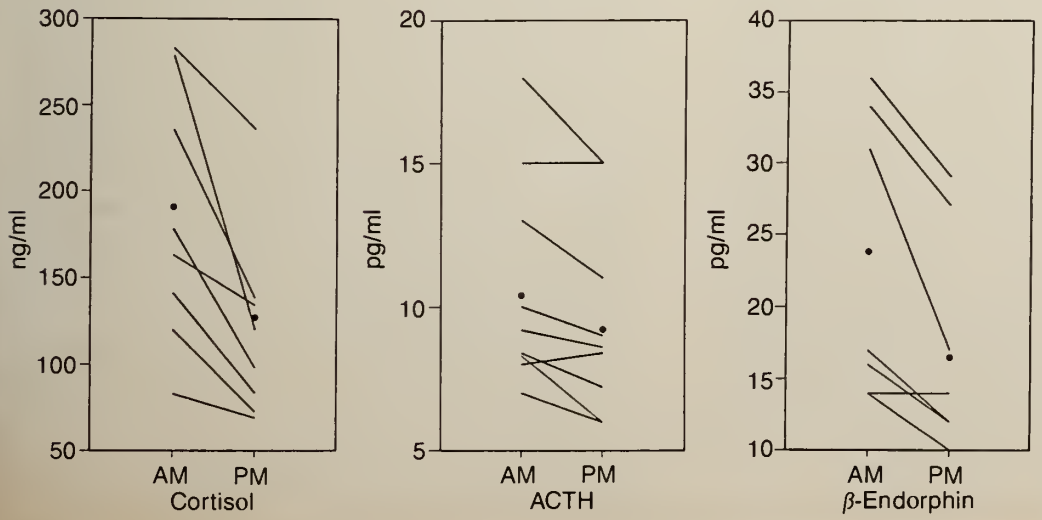

Figure 3.—Morning and afternoon concentrations of cortisol, adrenocorticotropin (ACTH), and β-endorphin are shown for 10 healthy adult human volunteers. • = mean

It would appear from this study that a diurnal rhythm exists in neonates in their first few days of life who are subjected to continuous artificial lighting and the care of a neonatal intensive care unit. This supports a study in adults by Dent and co-workers that indicated that the diurnal rhythm of immunoreactive β-endorphin does not appear to be closely associated with a specific sleep stage or to be related to the occurrence of sleep.[4] Our findings, however, do not agree with those of previous studies done of infants.[10,19] We fully recognize that specimens collected at only two specific time intervals may not be enough to confirm the existence or absence of a biologic rhythm, as the release of these hormones is episodic and depends on various other factors within a host. Further studies are needed to confirm these observations.

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Clinical Medicine

Prevalence of Myofascial Pain in General Internal Medicine Practice

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Myofascial pain is a regional pain syndrome characterized in part by a trigger point in a taut band of skeletal muscle and its associated referred pain. We examined a series of 172 patients presenting to a university primary care general internal medicine practice. Of 54 patients whose reason for a visit included pain, 16 (30%) satisfied criteria for a clinical diagnosis of myofascial pain. These patients were similar in age and sex to other patients with pain, and the frequency of pain as a primary complaint was similar for myofascial pain as compared with other reasons for pain. The usual intensity of myofascial pain as assessed by a visual analog scale was high, comparable to or possibly greater than pain due to other causes. Patients with upper body pain were more likely to have myofascial pain than patients with pain located elsewhere. Physicians rarely recognized the myofascial pain syndrome. Commonly applied therapies for myofascial pain provided substantial abrupt reduction in pain intensity. The prevalence and severity of myofascial pain in this university internal medicine setting suggest that regional myofascial pain may be an important cause of pain complaints in the practice of general internal medicine.

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Myofascial pain is a clinical syndrome of soft tissue pain arising from skeletal muscle. Specific criteria are evolving but include an active trigger point, which is a discrete tenderness in a taut band of skeletal muscle, and its associated regional referred pain.[1-7] A key to understanding the myofascial pain syndrome is that a patient's pain complaint is pain referred from skeletal muscle. Because of this, the pain site is usually distant from the causative active trigger point in skeletal muscle (Figure 1).[4,5,8,9] The pain is regional rather than generalized, and the referred pain patterns appear to be consistent and reproducible. Compressing the active trigger points characteristically intensifies the associated referred pain, and multiple trigger points can produce overlapping areas of referred pain.[6]

The mechanism of the referred pain symptoms in myofascial pain is not known, although the notion of referred pain from muscles and other tissues is well documented.[8,10] One possibility is the convergence of visceral and somatic sensory inputs onto pain projection neurons in the spinal cord.[11]

Recent studies have objectively documented several clinical features of myofascial trigger points. In one study, pressure algometry was found to be a reliable index of trigger point sensitivity.[12] In another study, the "stretch-and-spray" technique, a suggested therapy for myofascial pain, reduced trigger point sensitivity as assessed by pressure algometry and the referred pain as assessed by a visual analog scale.[13] Fricton and co-workers reported higher motor unit activity to a standard stimulus in electromyographic recordings taken within 2 cm of trapezius trigger points located in taut bands of muscle.[2] Modern detailed histologic and biochemical studies of trigger points from patients with unambiguous myofascial pain are lacking.

Clinical descriptions of the myofascial pain syndrome, under various terms, date back more than 100 years.[14,15] Good called attention to "anatomically defined muscular areas," now called trigger points, that resulted in referred pain syndromes.[7] Earlier, Kellgren had shown experimentally that referred pain could arise from muscle.[16] These ideas were brought together by Travell and Rinzler and others in studies delineating the typical pain referral patterns of active trigger points within many muscles.[4,8] A compendium of the pain referral patterns for many muscles has been published.[9]

The myofascial pain syndrome is the source of some controversy,[17-20] especially in its relationship to primary fibromyalgia, which is likely to be a distinct disorder. Despite this controversy, the clinical syndrome of myofascial pain as a regional pain complaint has been useful to many investigators and clinicians and has been reported as a cause of pain complaints in neurosurgery,[21] gynecology,[22] chronic pain,[23] physical medicine,[24] temporomandibular disorders,[25] headaches,[26] rheumatology,[27] neurology,[28] and pediatrics.[29] The recent interest in the myofascial pain syndrome is reflected by the National Library of Medicine's use of myofascial pain syndromes as an indexing term and by the inclusion of two specific myofascial pain syndromes in the taxonomy of pain published by the International Association for the Study of Pain.[3] While reviews of myofascial pain contend that it is

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common in general medical practice,[6] the prevalence and features of this clinical pain disorder in primary care internal medicine have not been reported.

To determine the importance of myofascial pain in the day-to-day practice of general internal medicine, we studied its prevalence and features in a primary care setting.

Patients and Methods

All English-speaking ambulatory patients scheduled for new evaluations or routine follow-up appointments with a resident physician at the UCLA Medical Ambulatory Care Center were eligible for the study. The Medical Ambulatory Care Center is a primary care general internal medicine group practice in a university teaching hospital. The practice provides both episodic and comprehensive care to patients from a wide range of socioeconomic strata. We enrolled every patient scheduled in 19 different half-day sessions between January 1986 and March 1987. All patients were asked by the receptionist to complete a brief questionnaire to determine if the reason for their appointment included pain. Patients chose among three statements to indicate the reason for their visit: pain, some other reason, or pain and some other reason. After informed consent and instruction, patients who indicated that the reason for their visit included pain were asked to complete a second questionnaire. Demographic data—age, sex, and insurance coverage—and the location, duration, and usual intensity of their pain were recorded. Patients with pain were asked to mark its location on a multiple-view body diagram. The usual pain intensity was measured by using a standard 10-cm visual analog scale.[30,31] The patients were not informed of the research question or given any information concerning myofascial pain or other muscle pain syndromes. Immediately after being seen and discharged by their regular physician, the study patients with pain were interviewed and examined by one of us (S.A.S. or B.J.) in a separate examining room without further involvement of the patient's physician.

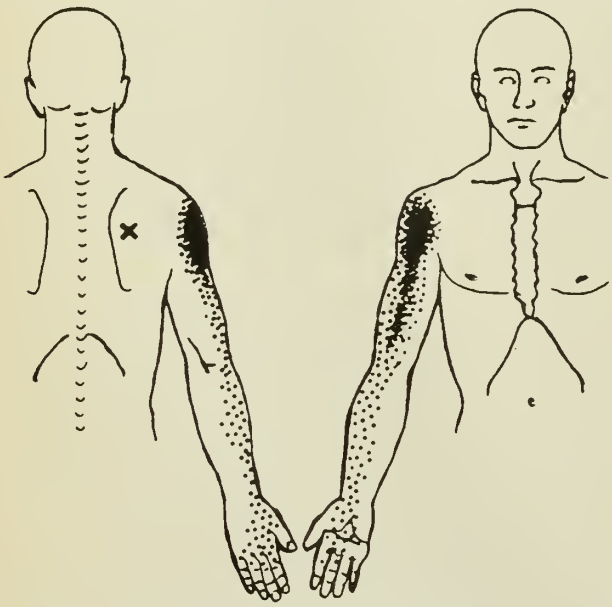

Figure 1.—An example of a regional referred pain due to the myofascial pain syndrome is shown. A referred pain pattern is represented by the shaded areas, and the typical location of the corresponding trigger point (X) is shown in the right infraspinatus muscle. The solid areas represent the predominant referred pain pattern, and stippled areas represent additional pain patterns. The typical patient complaint to a clinician would be "shoulder pain." Note that the region of pain is distant from both the involved muscle and the trigger point. Virtually identical patterns were reported by Sola and Kuitert,[4] Kellgren,[5] and Travell and Rinzler.[8] (Adapted from Travell and Simons.[9])

Guided by patients' pain descriptions and body diagrams, we systematically examined patients with pain to determine the cause of their pain. Patients with an acute or chronic medical diagnosis that adequately explained their pain—such as pharyngitis, neuropathy—had their diagnosis recorded after confirmation. Chart review and an interview with the patient and the patient's physician were used to determine other causes of pain.

Patients in whom a straightforward medical diagnosis could not be readily established had a detailed myofascial trigger point examination. In making the clinical diagnosis of myofascial pain, we correlated the patient's pain complaint with published pain referral patterns[9] to identify all muscles possibly harboring causative trigger points. Each of these muscles was examined for discretely tender points in bands of muscle (potential active trigger points), and, when found, these tender points were manually compressed for 5 to 20 seconds to see if the patient's pain complaint could be intensified. Thus, to make a clinical diagnosis of myofascial pain, we required that the patient have pain, that the pain pattern conform to the established referral maps, and that the trigger point examination intensify the patient's pain complaint. The muscles harboring the active trigger points were recorded. We excluded tender points that did not refer pain or that elicited a referred pain pattern but did not reproduce the patient's pain complaint.[32]

As part of the research evaluation, patients with the diagnosis of myofascial pain were treated by one of us (S.A.S. or B.J.) with either stretch-and-spray or trigger point injection[33-35] as currently described.[36] Study patients were not told that these methods represented treatment, only that the investigators were measuring any effect of them on their pain. Before treatment, patients with myofascial pain rated their pain intensity (the referred pain) by using a standard 10-cm visual analog scale. For stretch-and-spray therapy, the involved muscle was passively stretched for about 20 seconds, while four to six sweeps of vapocoolant spray (Fluori-Methane, Gebauer Chemical Company, Cleveland) were applied over the trigger point and into the area of pain referral. This procedure was repeated two more times at about one-minute intervals. For trigger point injections, the trigger point was located by direct palpation, disrupted by needle penetration, and injected with ½ to 1 ml of 0.5% procaine hydrochloride. Within five minutes of treatment, a posttreatment visual analog scale was again recorded.

We used microcomputers to analyze all data using commercially available data-base and statistical software (dBase III Plus, Ashton-Tate, Torrance, and Crunch Statistical Package, Crunch Software, Oakland, California). χ^2, Fisher's exact test, and the paired t test were used to determine statistical significance. A P value of less than .05 was considered statistically significant. Confidence intervals were calculated by standard methods.[37] Follow-up data were obtained by reviewing the medical charts. The study protocol was approved by the UCLA Human Subjects Protection Committee.

Results

A total of 201 consecutive patients were asked to participate in the study; 29 patients were excluded—17 refused to

participate and 12 did not speak English—leaving a study group of 172. The mean age of the patients was 53.5 ± 18.2 (1 standard deviation) years and 69% were women. The primary insurance coverage of the sample varied: 34% were covered by private insurance, 36% by Medicare, 23% by Medicaid (Medi-Cal), and 7% by other programs.

Of the 172 patients, 54 (31%) said that the reason for their visit included pain, with 23 reporting that pain was the primary reason and 31 including pain and some other reason.

Of patients with pain, 16 (30%; 95% confidence interval, 19% to 43%) fulfilled our criteria for myofascial pain, and 38 (70%) had pain due to other conditions (Table 1). Seven patients did not have a cause for their pain determined during the study interview and are listed as "not determined."

The age and sex were similar in the patients without pain (mean age, 54.3 ± 18.14 years, 68% female), patients with nonmyofascial pain (mean age, 51.5 ± 19.33 years, 68% female), and the patients with myofascial pain only (mean age, 52.2 ± 16.4 years, 75% female); for age, F (2 degrees of freedom) = 0.37, $P = .69$; for sex, χ^2 (2 *df*) = 0.34, $P = .84$.

The mean usual pain intensity as measured by a visual analog scale was high and somewhat greater for patients with myofascial pain as compared with patients with other causes of pain (51.25 ± 23.8 versus 42.9 ± 22.3). The observed difference in mean pain intensities by the visual analog scale is 8.35 units higher for the myofascial pain patients (95% confidence interval, 22.24 to −5.54 units). Because of the high baseline value, a difference of −5.54 visual analog scale units between groups would not be clinically significant. These data suggest that the mean pain intensity of myofascial pain is comparable to, or possibly greater than, pain due to other causes.

Almost half (23/54) of patients presenting with pain said that pain was the only reason for their visit. Pain was the only reason for 7 (44%) of 16 patients found to have myofascial pain and 16 (42%) of 38 patients with pain of other causes.

The duration of myofascial pain varied: four patients (25%) had pain for a month or less, three patients (19%) had pain for 1 to 6 months, four (25%) patients had pain 6 to 12 months, and five (31%) reported pain for more than a year.

Of 22 patients with complaints of upper body pain—headache, head pain, neck, shoulder, upper back—13 had myofascial pain compared with 3 of 29 with pain located elsewhere (Fisher's exact test, $P < .0003$). Complaints of lower back pain were uncommon, reported by only three (6%) patients with pain.

The 16 patients with myofascial pain had the following pain complaints and muscles harboring the active trigger points: three "headache" (3 sternocleidomastoid), five "neck" or "shoulder" pain (3 infraspinatus, 1 sternocleidomastoid, 1 levator scapulae), five "upper back" pain (3 middle trapezius, 1 scalene, 1 upper paraspinal), two "low back" pain (2 lower paraspinal), and one "chest" pain (1 oblique).

We treated 14 patients specifically for myofascial pain (2 patients refused treatment), 12 with the stretch-and-spray technique, and two with trigger point injections. In these 14 patients with myofascial pain, the mean pain intensities assessed in visual analog scale units decreased significantly from 54.7 (pretreatment) to 26.1 (posttreatment; paired differences *t* test, $P < .001$). Only two patients had such treatments initiated by their primary care provider.

Illustrative case. The patient, a 48-year-old man, was seen for a new patient evaluation of intermittent anterior shoulder pain for three to four months, worsened by travel. The sole reason for his visit was this pain. His past history was noncontributory. On examination he had an active trigger point in the infraspinatus muscle (Figure 1) that reproduced his anterior shoulder pain. Stretch-and-spray therapy reduced the pain intensity from 64 to 31 as assessed by the visual analog scale. Following this initial treatment, the patient was informed of the reason for his pain and given a home stretching program.

All patients with myofascial pain have been followed up a median of 16 months (range, 7 to 24) by chart review except for three patients who were observed for only a month. No other cause of pain has been diagnosed in these patients.

TABLE 1.—*Reason for Visit and Cause of Pain Complaint*

	Patients, No.
Reason for Visit (n=172)	
Pain	23
Some other reason	118
Pain and some other reason	31
Cause of Pain Complaint (n=54)	
Myofascial pain	*16*
Other causes	*38*
Gastrointestinal	7
Infection*	7
Arthritis	5
Angina	3
Neuropathy	3
Other†	6
Not determined	7

*Includes cystitis (2), pharyngitis (2), cellulitis, bronchitis, and herpes zoster.
†Includes 1 each benign tongue lesion, bone contusion, cervical stenosis, costochondritis, and 2 wound site pain.

Discussion

By investigating regional pain complaints, we made the clinical diagnosis of myofascial pain in nearly 30% of patients with pain seen. Thus, in our setting, the prevalence of the myofascial pain syndrome was high, and it represented the single most common reason for the study patients with pain to visit their physician.

We think our estimate of myofascial pain prevalence is valid and that it does not suffer from reporting bias as the patients, rather than the physicians, identified pain as the reason for the visit. We also used specific criteria for the clinical diagnosis of referred myofascial pain.

We found the predominant pain complaint in the patients with myofascial pain could be ascribed to a single muscle. For example, many patients with shoulder pain had this complaint as the result of an active trigger point in the infraspinatus muscle. This finding supports the notion that the myofascial pain syndrome can be viewed as a process related to individual muscles.

We had no difficulty in relating pain symptoms to published maps of referred pain patterns and then locating active trigger points in muscle. We also found that suggested therapies were effective immediately and that during 16 months of follow-up, no other cause of pain was noted in the medical record. Thus, despite the fact that the syndrome of myofascial pain remains somewhat controversial,[17,20] our data suggest that the myofascial pain syndrome is relevant to primary

care internal medicine. Additional studies of prevalence in other general internal medicine settings should be done to validate our findings.

Myofascial pain appears to be a clinically important problem. In addition to the high prevalence, 75% of our myofascial pain patients reported symptoms for at least a month, and the mean intensity of their pain, as assessed by the visual analog scale, was comparable to or possibly greater than the intensity of other pain complaints that brought study patients to see their physicians. Finally, 44% of the myofascial pain patients reported that pain was the only reason for their visit.

Some of our study patients may have had pain for relatively long periods of time because of a poor recognition of the myofascial pain syndrome. Only one primary care provider caring for two of the study patients correctly determined the nature of the patients' pain complaints and initiated specific therapy.

We were surprised by the relatively infrequent complaint of "low back" pain. In a national study of ambulatory pain,[38] the most common pain complaint was low back pain; that study, however, relied on a physician, not the patient, to record the reason for the visit. Our findings may differ because patients identified not only pain as the reason for their visit but also the specific painful area to be examined. Because we asked for the reason for the visit to the physician that day, patients may have preferentially indicated important pain or previously unexplained pain.

The recommended treatment of myofascial pain includes identifying and correcting perpetuating factors, the use of physical therapy, a home stretching program,[26] and stretch-and-spray and trigger point injections.[36] Additional studies of treatment with long-term follow-up are needed, however. Although the primary purpose of our study was to determine the prevalence and clinical features of myofascial pain in our practice, we were also interested to see if commonly suggested therapies would be useful in our subjects. Treatment did provide some immediate relief, and the amount of relief obtained was similar in magnitude to that of other reports.[13]

The prevalence, severity, and duration of myofascial pain syndromes observed in this study suggest that this may be an important cause of regional pain complaints in patients seeking primary care from internists. Additional research is needed to more fully characterize this syndrome.

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Clinical Review

Myelodysplastic Syndromes

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The myelodysplastic syndromes are a heterogeneous group of hematopoietic stem cell disorders characterized by dysplastic and ineffective hematopoiesis and a varying risk of transformation to acute leukemia. Although the natural history of these syndromes is variable, several factors appear to be of prognostic importance, including the French-American-British classification, the karyotype, in vitro colony formation, and others. The pathogenesis of the myelodysplastic syndrome is not known, but recent evidence suggests that alterations of cellular oncogenes may be a causative factor. There is no standard therapy for myelodysplasia, and thus novel approaches to patient management are warranted.

(Doll DC, List AF: Myelodysplastic syndromes. West J Med 1989 Aug; 151:161-167)

The myelodysplastic syndromes are a heterogeneous group of hematopoietic stem cell disorders characterized by ineffective and dysplastic hematopoiesis.[1,2] Most patients are older than 60 years and characteristically have peripheral cytopenia(s) with a normocellular or hypercellular bone marrow. Leukemic transformation is not uncommon, but even in its absence, a myelodysplastic syndrome may be a lethal hematologic disorder with death from infection and bleeding[3] arising from cytopenia or impaired function of neutrophils[4] and platelets.[5] Although this syndrome may occur as a late complication of chemotherapy or radiotherapy,[6] the cause(s) of de novo myelodysplasia remains obscure. The treatment of these syndromes remains unsatisfactory, but promising new therapeutic regimens have recently been used in an attempt to restore normal hematopoiesis.[7]

Classification and Diagnosis

Numerous terms have been applied to describe the myelodysplastic syndromes, including preleukemia, hematopoietic dysplasia, refractory anemia, refractory normoblastic anemia, refractory anemia with an excess of myeloblasts, subacute myeloid leukemia, oligoblastic leukemia, dysmyelopoietic syndromes, smoldering leukemia, myeloid dysplasia, and primary acquired panmyelopathy with myeloblastosis. Such diverse terminology and a lack of uniform criteria for these disorders have resulted in inevitable difficulties in classification and in predicting the disease outcome. In 1982 the French-American-British (FAB) Cooperative Group addressed this problem and proposed a morphologic classification system encompassing the spectrum of diseases.[1] As shown in Table 1, five subtypes of the syndromes have been described: refractory anemia; refractory anemia with ring sideroblasts; refractory anemia with an excess of blast forms; refractory anemia with an excess of blast forms in transformation; and chronic myelomonocytic leukemia. Although several investigators have questioned the need for and validity of this new scheme, it has enjoyed widespread acceptance because of its reproducibility and has been found useful for comparing studies among different institutions. The results of several recent studies that have classified their cases according to this system are given in Table 2.[3,8-18] Some investigators included cases in their analysis associated with cytotoxic chemotherapy or radiotherapy,[8,9,18] and others included only patients with de novo myelodysplasia.[3,10-17] Also, several investigators found it difficult to categorize particular patients in specific subtypes and noted that transitions and combinations existed in individual patients.[9-11,18]

The clinical diagnosis of a myelodysplastic syndrome can often be made by visually inspecting the bone marrow aspirate and peripheral blood smear and detecting various dysplastic changes in each hematopoietic lineage.[1,2,19] The examination of bone marrow specimens from trephine biopsies,[20] chromosome analysis,[13,15-17,21,22] in vitro hematopoietic stem cell assays,[16,23] and flow cytometry[24] may provide additional supportive evidence. Investigating the oncogene expression at the first clinical signs of the syndrome and throughout the progression of disease would also be of interest.[25] Such specialized investigations may be particularly useful to confirm the diagnosis in those patients with minimal hematologic or morphologic changes. Moreover, these tests may be useful in predicting the clinical outcome (vide infra).

The cytopenia(s) that direct attention to the disorder should be confirmed as a persistent feature, unassociated with any other systemic disorder such as renal or hepatic failure or ethanol abuse. Vitamin B_{12} and folate deficiency should be excluded. In addition, a detailed occupational history for exposure to potential carcinogens and a previous history of treatment with cytotoxic drugs or radiotherapy should be elicited.

Clinical and Laboratory Manifestations

The exact incidence of de novo myelodysplasia is unknown; it is not uncommon in the elderly population, however. For instance, 174 patients with the syndromes were seen at the Mayo Clinic during a three-year period.[17] Juneja

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ABBREVIATIONS USED IN TEXT

CSF = colony-stimulating factor
FAB = French-American-British [Cooperative Group]
G6PD = glucose-6-phosphate dehydrogenase

and co-workers saw 118 new cases of these disorders during a similar time span compared with 126 new cases of acute myeloid leukemia.[10] The myelodysplastic syndromes occur in a middle-aged to elderly population, with the median age in most series being about 65. Cases diagnosed before age 50 are uncommon, and there is a male predominance.[1,2,16,19] Most patients are seen because of weakness, fatigue, or pallor due to anemia. Some patients seek advice because of bleeding, easy bruising, or infection. Hepatomegaly, splenomegaly, and lymphadenopathy are infrequent findings on a physical examination.

The hematologic abnormalities in these disorders have been extensively described[1,2,8-11,19] and are summarized in Table 3. It should be emphasized that such findings are pleomorphic and are not in and of themselves diagnostic; they may be susceptible to subjective interpretation, and other disorders must be excluded.

Most patients with the syndromes are anemic with an inappropriately low reticulocyte response. The erythrocytes are usually normocytic or macrocytic, although patients may present with microcytosis, hypochromia, and reticulocytosis.[26] Anisocytosis, poikilocytosis, basophilic stippling, and megaloblastoid nucleated erythrocytes may be seen. Such peripheral blood findings are characteristically associated with dyserythropoietic features in bone marrow progenitors with both nuclear and cytoplasmic abnormalities. These may include erythroid hyperplasia with megaloblastoid features, nuclear budding, multinucleation, karyorrhexis, and vacuolization of the cytoplasm. Ringed sideroblasts can usually be found in a varying proportion of normoblasts. Abnormalities of erythrocyte glycolytic enzymes,[27] increases in hemoglobin F levels,[28] alterations in blood group antigens,[29] and paroxysmal nocturnal hemoglobinuria-like defects[30] have been described. Acquired hemoglobin H disease has also been noted.[31]

Leukopenia, usually due to absolute neutropenia, is found in about half the patients at the time of diagnosis. Granulocytes may show reduced segmentation—the pseudo-Pelger-Huët abnormality—or reduced or absent granulation. Circulating myelocytes and blast cells may be detected

TABLE 1.—*Classification of the Myelodysplastic Syndromes*

FAB Classification	*Blasts in Bone Marrow, %*	*Other Findings*
Refractory anemia (RA)	<5	<1% circulating blast cells
RA with ring sideroblasts	<5	<1% circulating blast cells; 15% ring sideroblasts in bone marrow
RA with excess blasts	5-20	<5% circulating blasts
Chronic myelomonocytic leukemia	<20	1×10^9/liter monocytes and promonocytes in peripheral blood
RA with excess blasts in transformation	20-30	5% circulating blast cells; Auer rods

FAB=French-American-British

TABLE 2.—*Diagnostic Subtypes of the Myelodysplastic Syndromes*

Source	*Patients, No.*	*Refractory Anemia*	*RARS*	*CMML*	*RAEB*	*RAEB-T*
Gold et al, 1983[16]	34	2	0	10	22	0
Juneja et al, 1983[10]	118	9	43	0	66	0
Weisdorf et al, 1983[3]	74	30	23	1	9	11
Foucar et al, 1985[8]	109	13	22	11	41	22
Knapp et al, 1985[15]	167	43	38	11	69	6
May et al, 1985[11]	39	9	15	4	9	2
Tricot et al, 1985[12]	85	25	12	11	14	23
Vallespi et al, 1985[9]	101	32	15	21	12	21
Jacobs et al, 1986[17]	46	14	8	10	9	5
Kuriyama et al, 1986[14]	50	25	7	8	10	0
Yunis et al, 1986[13]	56	13	13	3	23	4
Group Français, 1987[18]	761	131	107	129	329	65
Total	1,640	346	303	219	614	159

CMML=chronic myelomonocytic leukemia, RAEB=refractory anemia with excess blast forms, RAEB-T=refractory anemia with excess blast forms in transformation, RARS=refractory anemia with ring sideroblasts

TABLE 3.—*Morphologic Abnormalities in Myelodysplastic Syndromes*

Lineage	*Peripheral Blood*	*Bone Marrow*
Erythroid	Macrocytes; ovalocytes; basophilic stippling; nucleated erythrocytes; poikilocytosis and anisocytosis; acanthocytes	Megaloblastoid erythropoiesis; nuclear budding; multinucleation; ringed sideroblasts; karyorrhexis; nuclear fragments; cytoplasmic vacuolization
Myeloid	Hypersegmentation; pseudo-Pelger-Huët anomaly; vacuolization; paramyeloid cells; abnormal or deficient granulation; nuclear tags	Defective granulation; partial maturation arrest at myelocyte stage; increase in monocytoid forms
Megakaryocytic	Agranular or giant platelets	Micromegakaryocytes; large mononuclear forms; multiple small nuclei

but generally constitute fewer than 5% of the leukocyte differential. Auer rods are rare. The neutrophil myeloperoxidase activity is decreased in some patients,[4] and there may be an increase in monocyte-specific esterase.[32] Granulocytes may also show defective phagocytosis, bactericidal activity, adhesion, and chemotaxis,[4] leading to a reduced resistance to infections. These features may have a common cytogenetic basis attributable to a partial or complete loss of chromosome 7.[33] Impaired myeloid maturation is readily detected on inspecting the bone marrow aspirate, which typically shows an increased percentage of granulocytic precursors, and a "maturation arrest" is often noted at the myelocyte stage.

Thrombocytopenia is seen in about 50% of patients with the myelodysplastic syndromes, and the platelets may be abnormal in both morphologic features and function. Abnormal megakaryocytes, including micromegakaryocytes, large mononuclear forms, and megakaryocytes with multiple small nuclei, are common bone marrow findings.[1,14] Indeed, Kuriyama and associates suggested that micromegakaryocytes detected in the marrow coupled with pseudo-Pelger-Huët anomalies in the peripheral blood smear represent the most specific features supporting the diagnosis of the syndrome.[14]

The lymphoid system may also be affected in patients with these syndromes, and it has been shown that the abnormal cells may be derived from the same clone as the pathologic erythroid and myeloid cells.[34] Lymphopenia with a reduced number of T-helper cells has been reported.[35] Natural killer cells may be reduced in number, and there may be an inadequate production of interferon and a failure of natural killer cells to respond to interferon. Abnormalities of T- and B-cell function have been noted.[36] Lastly, a high incidence of immunologic abnormalities such as monoclonal gammopathy and autoantibodies[37] and coexistent lymphoid or plasma cell neoplasms have been shown in these patients.[38]

Cytogenetic Abnormalities

Using standard techniques of karyotype analysis, clonal chromosomal aberrations have been detected in about a third to half of patients with de novo myelodysplasia.[3,12,15-17,21] Using refined chromosome banding techniques, however, Yunis and colleagues reported that 73% of patients with these syndromes had a cytogenetic defect.[13,39] Moreover, these identified prognostic subgroups of the disorder.[13,39]

The chromosome abnormalities follow a nonrandom pattern and are similar to those found in treatment-induced acute myelogenous leukemia.[21] The abnormal clone can replace normal hematopoiesis partially or completely. As shown in Table 4, the most frequent cytogenetic abnormalities in the myelodysplastic syndromes involve structural or numeric abnormalities of chromosomes 5 and 7 and trisomy 8.[21] Other findings include a reduplication of chromosome 9, expressed +9, 21 (+21), or the long arm of chromosome 1; a deletion of chromosome 20 (−20); and an isochromosome 17 (i17). Complex chromosomal abnormalities occur in some patients and are more frequent in secondary myelodysplasia.[39,40] Such cytogenetic findings support the notion that these syndromes are clonal in nature. It is noteworthy that certain chromosomal abnormalities found in acute myelocytic leukemia are rarely found in the myelodysplastic syndromes, suggesting that in patients with these aberrations, the disease did not develop from preexisting myelodysplasia.

TABLE 4.—*Frequent Chromosome Abnormalities in Myelodysplastic Syndromes**

Chromosome Abnormality	*Incidence, %*
−5/5q−	10-20
−7/7q−	15-25
+8	15-20
20q−	7-10

*q represents the long arm of a chromosome, + represents a duplication of a chromosome or chromosome segment, and − represents a deletion of a chromosome or chromosome segment.

These include the 8:21 translocation often found with type M2 of the FAB classification, translocation (15:17) associated with acute promyelocytic leukemia, and translocation (9:22) of chronic granulocytic leukemia.

Chromosome abnormalities in patients with the myelodysplastic syndromes may be associated with a shortened survival and an increased risk of evolving to acute leukemia.[13,16,17,22,39] Although new clonal karyotypic abnormalities have emerged in association with an increase in the percentage of blasts in the bone marrow on leukemic progression,[22] most patients with these syndromes do not show chromosome abnormalities at the time of transformation to overt acute myelocytic leukemia.[22] Of note is that specific cytogenetic changes, such as deletion in the long arm of chromosome 5 (5q−),[41] or monosomy 7 (−7),[42] may be associated with distinct clinicopathologic syndromes. Whether chromosome abnormalities are involved in the pathogenesis of myelodysplasia remains to be elucidated.

Pathogenesis

Although the cause(s) of the myelodysplastic syndromes is unknown, evidence from cytogenetic studies[21] and glucose-6-phosphate dehydrogenase (G6PD) isoenzyme analyses[34,43] indicates that they are clonal disorders of pluripotent stem cells. G6PD studies have shown that Epstein-Barr virus-transformed B lymphoblastoid lines, derived from a patient with the syndrome, showed restricted G6PD isoenzyme expression.[43] Similarly, Prchal and co-workers found that T and B lymphocytes from a patient with idiopathic sideroblastic anemia were derived from the same clone as the myeloid elements.[34] Further support for the involvement of the pluripotent stem cell is provided by reports of myelodysplasia evolving to acute lymphoblastic[44] or acute leukemia showing mixed lymphoid-myeloid features.[45]

Raskind and associates suggested that the myelodysplastic syndromes arise by a multistep process. They proposed that at least two events are involved in their pathogenesis, one promoting proliferation of a clone of genetically unstable pluripotent stem cells and another inducing chromosomal abnormalities in its descendants.[43] This sequence would explain the abrupt evolution to acute leukemia in patients after a prolonged period of apparent hematologic stability.

A multistage mechanism for inducing malignancy has been shown for various tumors in many species, and oncogenes may have an important role in the process.[46] In the mouse embryo fibroblast cell line, for example, the *ras* oncogene is unable to transform fibroblasts unless they have first entered a proliferative state. If, however, both the C-*myc* and *ras* oncogenes are transfected together, a malignant transformation results.[47] Thus, single insults by themselves do not

produce a malignant transformation, but a succession of two events may.[46]

Although the significance of chromosomal changes in malignant cells is still not fully understood, there is increasing evidence that chromosomal rearrangements are instrumental in activating cellular oncogenes.[48] As noted earlier, karyotypic aberrations are frequent in the myelodysplastic syndromes and most commonly involve chromosomes 5, 7, and 8. Chromosome 5 carries two known oncogenes, c-*fos* and c-*fms*, on its long arm; chromosome 7 contains the oncogene erb_β; and chromosome 8, c-*myc*.[49] Furthermore, three oncogenes—*ras, myc,* and *fos*—have been directly implicated in growth factor-mediated signaling mechanisms,[50] and, as suggested by Duel and Huang,[51] any genes that code for proteins influencing the cellular response to growth factors represent potential oncogenes. Abnormalities in the expression of these genes, whether resulting from deletion, duplication, abnormal activation, suppression, or mutation, can result in a change in the control of proliferation, which may contribute to the malignant process. Indeed, an activated N-*ras* oncogene in patients with deletion of the long arm of chromosome 5 has been shown during a leukemic progression from myelodysplasia.[52]

Thus, an initiating event may be speculated in these syndromes, perhaps activation of a cellular oncogene, that triggers the proliferation of an abnormal clone. The expanding clone may become immortalized by the loss of normal control mechanisms governing the synthesis of DNA or autonomy from normal growth inhibitory factors (or both). Results of in vitro studies indicate that the malignant clone may also inhibit normal hematopoiesis. Depending on the genetic instability and proliferative capabilities of the clone, myelodysplasia may progress to overt acute myelocytic leukemia. The role of oncogenes, antioncogenes, growth factors, chromosomal aberrations, and stromal cells in the pathogenesis of these disorders needs further evaluation.

Management

The treatment of the myelodysplastic syndromes has in general been disappointing. Most patients with these disorders are elderly and may have other morbid medical problems that complicate therapeutic decisions. Because these syndromes comprise a heterogeneous group of disorders with varying clinical courses, a period of observation with close monitoring of blood cell counts and sequential marrow examinations is the mainstay of the initial management. Some patients, particularly those with refractory anemia or refractory anemia with ring sideroblasts, may have an indolent course, and no treatment may be required. Other patients may require blood transfusions to alleviate the symptoms of anemia or antibiotics for internal infection. For those patients who have an aggressive clinical course, however, more intensive therapy should be considered.

Despite evidence of megaloblastosis, initial supplementation with vitamin B_{12} or folic acid is generally not beneficial. Although a subset of patients with sideroblastic anemia may respond to the administration of pyridoxine hydrochloride or pyridoxal-5-phosphate,[53] most patients show no improvement. Nevertheless, a therapeutic trial of pyridoxine, 300 mg daily, should be considered in patients with sideroblastic anemia. Similarly, corticosteroid therapy is not useful in most patients, although in vitro cortisol-enhanced colony growth may identify a small subset of patients who might benefit from such therapy.[54] In view of their possible added toxicity and the low frequency of response, corticosteroids should not be used as empiric therapy.

The use of androgens has also proved ineffective in these patients.[55] Danazol, a synthetic attenuated androgen, has recently been reported to have activity in patients occasionally seen who have this syndrome and concomitant immune thrombocytopenia or hemolysis.[56] In the usual patient with a myelodysplastic syndrome who has marrow dysfunction, we and others have not found this agent to be useful.[57,58]

13-*cis*-Retinoic acid, a stereoisomer of retinoic acid, has also been used in patients with this syndrome.[59-63] In vitro studies have shown that retinoic acid inhibits tumor cell growth and also induces differentiation in various tumor cell lines,[64] including the human promyelocytic leukemia cell line HL-60.[65] Retinoids stimulate the growth of normal erythroid progenitors in vitro and increase granulopoiesis.[65] Based on these findings, several uncontrolled clinical trials using 13-*cis*-retinoic acid in these patients have been reported.[59-62] In general, the studies have shown a low response rate, and all responses were partial, of short duration, and accompanied by moderate dermatologic or hepatic toxicity.[59-62] Moreover, the drug had to be given for at least three weeks and sometimes several months before a response was seen. Recently a randomized study comparing the use of 13-*cis*-retinoic acid with placebo in patients with this disorder showed no beneficial effect.[63] Hence, *cis*-retinoic acid is not recommended for routine clinical practice. The efficacy of other retinoids with less toxicity merits evaluation.

Intensive cytotoxic treatment, such as that used in cases of acute leukemia, has also been employed partially in patients with high-risk subtypes, such as refractory anemia with excess blast forms, with blast forms in transformation, and chronic myelomonocytic leukemia.[66] The regimens used varied, but most included cytarabine (cytosine arabinoside) hydrochloride and an anthracycline. The response rate ranged from 15% to 53%, with complete remission seen primarily in those patients younger than 50 years.[66,67] In the series reported by Tricot and Boogaerts, six of seven patients younger than 50 years achieved complete remission compared with only two of eight patients in the older age group.[67] Of note is that all eight patients had a completely normal karyotype at the time of complete bone marrow remission. Thus aggressive combination chemotherapy may be of value in younger patients with specific subtypes of primary myelodysplasia. Whether such therapy has a significant impact on the survival of these patients has not yet been determined.

Most recently, several investigators have used low doses of cytarabine in the treatment of these syndromes.[68-71] The dosages ranged from 5 to 20 mg per m^2 of body surface daily by continuous intravenous infusion or subcutaneous injection. Although notable responses were recorded in approximately 60% of patients, they were generally partial and of short duration, usually not exceeding five months. Second and third responses may be achieved with the same regimen after an initial relapse.[68] Even with low-dose regimens, however, toxicity was substantial, with about 50% of patients experiencing a major complication, such as sepsis or hemorrhage.

Whether low-dose cytarabine acts by inducing cellular differentiation or by a cytotoxic mechanism is controversial.[72] When an abnormal clone can be identified by cytogenetic studies, treatment with low-dose cytarabine (ara-C)

results in suppression of this clone rather than maturation,[73] suggesting that a response is achieved primarily by a cytotoxic effect rather than differentiation. Any advantage of low-dose ara-C over standard-dose cytarabine regimens remains to be determined. In light of its considerable toxicity and short duration of response, the use of low-dose ara-C cannot be recommended for routine clinical practice.[74]

Additional therapeutic methods that merit consideration in the treatment of these syndromes include bone marrow transplantation,[75] azacitidine (5-azacytidine), biologic response modifiers,[76] vitamin D_3,[77] haem arginate,[78] and colony-stimulating factors (CSFs).[79] The recent cloning of CSFs has made large amounts of the purified protein available for investigational use.[80,81] Preliminary results suggest that granulocyte CSFs can induce the differentiation of myeloid leukemia cells in vitro[81] and that infusing human granulocyte-macrophage CSFs into primates stimulates a pronounced leukocytosis and reticulocytosis.[82] A phase I study using recombinant granulocyte-macrophage CSFs in patients with the myelodysplastic syndromes showed short-term improvement in hematologic variables in some patients.[83] Future trials in these syndromes should evaluate combinations of differentiating agents with cytotoxic drugs, interferons, tumor necrosis factor, and colony-stimulating factors.[84-89]

Course and Prognosis

The natural history of this disorder varies widely, with some patients having an indolent clinical course, whereas others will succumb during the first year.[3,9,12] Although acute leukemia will eventually develop in a substantial portion of patients (12% to 38%), an even larger percentage (30% to 63%) will succumb to complications resulting from bone marrow failure.[3,12] In rare cases, myelodysplasia will terminate in acute myelofibrosis[10] or in a syndrome simulating malignant histiocytosis.[90]

Several factors have been reported to influence the prognosis in these syndromes. The FAB classification appears to be the most important prognostic marker. For example, concomitant neutropenia, thrombocytopenia, or both are less prevalent in patients with refractory anemia with ring sideroblasts, and the disease seldom evolves into acute leukemia. The median survival in patients with this subtype generally exceeds 60 months.[8,12,91] In contrast, chronic myelomonocytic leukemia is associated with a poor prognosis, with a median survival of about 18 months.[91,92] For the other three subtypes, the rising marrow blast-cell number is associated with an increased mortality and a heightened risk of leukemic transformation.[8-13,91,93] Hence, the median survival for these disorders ranges from greater than 30 months in refractory anemia, to 11 months in refractory anemia with an excess of blast forms, and 5 months in refractory anemia with an excess of blast forms in transformation.[8-13,91]

According to most investigators, karyotypic findings provide an additional prognostic measure.[13,15-17,39,93] An abnormal karyotype, in particular complex chromosome abnormalities, confers a higher risk of leukemic evolution and therefore a shorter survival.[13,15-17,39,93] In this regard, Yunis and colleagues recently proposed prognostic subgroups of the myelodysplastic syndromes based on cytogenetic findings.[39] They reported that patients with a normal karyotype or isolated monosomy 5 had a relatively favorable prognosis. In contrast, patients with trisomy 8, monosomy 7, or complex defects had a poor prognosis. In addition to karyotype analysis, determining the DNA content of bone marrow cells by flow cytometry may also yield important prognostic information.[24]

A third discriminatory factor is based on the peripheral blood findings, with multilineage defects associated with a poor prognosis.[3,8,10,12,91,93] Mufti and co-workers suggested a scoring system for predicting disease outcome.[91] A score of 1 is assigned for each of the following presenting features: bone marrow blasts of more than 0.05 (5%), platelets of less than 100×10^9 per liter (100,000 per μl), neutrophils of less than 2.5×10^9 per liter (2,500 per μl), and hemoglobin less than 6.21 mmol per liter (10 grams per dl). Patients with a score of 4 had a median survival of only 8.5 months, those with a score of 0 or 1 had a median survival of 62 months, and those with a score of 2 or 3 had a median survival of 22 months. Other investigators have also proposed a scoring system for these disorders.[94,95]

Another prognostic factor is the in vitro myeloid growth pattern. Patients with nonleukemic in vitro growth patterns have a 21% to 40% incidence of transformation to acute leukemia and a median survival of 9 to 50 months. In contrast, persons with leukemic growth patterns have had a 50% to 80% incidence of transformation and 5 to 10 months' median survival.[23] There is no correlation of in vitro growth patterns with the FAB classification.

Other factors that have been reported to adversely affect survival include a high percentage of abnormal metaphases,[16] the presence of large clusters or an inability to culture granulocyte-macrophage colonies,[36,93] the number of ringed sideroblasts,[96] and the central clustering of immature myeloid precursors in the bone marrow matrix rather than adhering to the endosteal surface.[97] Such prognostic factors should be considered in choosing therapy for patients with the myelodysplastic syndromes.

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Pediatric Fluid Loss

ONE PRETTY GOOD SIGN of how sick children are happens to be their capillary refill. We all know about capillary refill in a child. You squeeze a thumbnail and you say "capillary refill," and by the time you've said the last "l," the fingernail should be red again. If you press the fingernail, release it, say "capillary refill" and it's still white, this child probably has a very low blood pressure level and is verging on shock. So, always press on the child's fingernail when you are trying to estimate fluid loss.

—WILLIS A. WINGERT, MD

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Clinical Review

Pregnancy and Inflammatory Bowel Disease

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Conclusions about the relationship between the pathophysiology and treatment of inflammatory bowel disease and the physiology and management of pregnancy are based on the results of several large physician surveys and retrospective chart reviews. Patients with active disease fare worse than those with inactive disease. There is little evidence that pregnancy affects the course of inflammatory bowel disease or that inactive inflammatory bowel disease affects the course of pregnancy. Judicious medical therapy is effective in controlling inflammatory bowel disease during pregnancy. Sulfasalazine or steroid therapy should not be withdrawn in a patient who needs it to achieve or maintain a quiescent state of inflammatory bowel disease during the course of pregnancy. Immunosuppressive therapy should be avoided. Aggressive medical therapy with total parenteral nutrition in a team approach with a gastroenterologist, surgeon, and perinatologist usually avoids the need for surgical intervention during pregnancy with a good fetal outcome in a patient whose disease is active. Contraception against pregnancy need only be considered in those patients whose disease is so severe that operative therapy is imminent.

(Zeldis JB: Pregnancy and inflammatory bowel disease. West J Med 1989 Aug; 151:168-171)

Issues relating to fertility and pregnancy are a major concern of patients with inflammatory bowel disease (IBD). A more optimistic appraisal about the relationship between pregnancy and IBD than was first thought is the result of the earlier diagnosis of IBD, a greater awareness by physicians of the nutritional needs of their patients, advances in prenatal care and fetal monitoring, progress in radiologic techniques, and an increased understanding of the natural history of the disease. Much can be concluded based on the experience of several large retrospective series and surveys. In this review I discuss the current thinking about many of the issues around fertility, pregnancy, and inflammatory bowel disease.

Inflammatory Bowel Disease and Fertility

Recent studies have shown that ulcerative colitis does not affect fertility.[1-3] Other studies that found reduced fertility were probably flawed owing to short follow-up periods, patient selection, and an inadequate medical control of the disease[4,5] or inadequate numbers of patients observed.[6]

The effect of Crohn's disease on fertility is controversial. Earlier investigations found that fertility was reduced.[7,8] These studies did not take into account the birth control practices of women who followed the advice of their physicians that IBD adversely affects pregnancy and that pregnancy could exacerbate IBD. A study of 40 women with Crohn's disease has suggested that women might have been "subfertile" and that they became fertile after the surgical resection of their involved viscera.[8] The authors did not discuss whether fertility in these women correlated with their nutritional status before and after their operations. In general, studies have failed to consider whether severe perineal problems affect fertility. A small percentage of women with Crohn's disease will have fistulization to fallopian tubes or tubo-ovarian abscesses that render them permanently sterile.

Khosla and co-workers found that the infertility rate of 112 married women with Crohn's disease was similar to that in the general population.[9] The results of a case-control study of 275 women with Crohn's disease from five European countries are in sharp contrast to those of Khosla and associates.[10] Mayberry and Weterman determined whether the patients were using birth control, were having sexual relations, and were advised by their physicians not to become pregnant. Patients with Crohn's disease had a notable reduction in the number of children born and a substantial increase in the incidence of prematurity. The rate of miscarriage and cesarean section was unaffected by Crohn's disease. The site of the disease did not affect these findings. Although 40 women with Crohn's disease were told not to have children, the women used birth control less but still had fewer pregnancies.

Sulfasalazine treatment causes oligospermia, reduced sperm motility, and an increased proportion of abnormal morphologic features of sperm. This is manifested as decreased fertility. Withdrawing sulfasalazine reverses these defects to normal, and patients presumably return to pretreatment fertile states.[11-14] The consequences of long-term sulfasalazine therapy on male fertility remain to be fully assessed.

In contrast to the results of total colectomies in men for cancer, proctocolectomy for ulcerative colitis rarely results in permanent impotence (1.5% in a series of 130 patients), temporary impotence, or retrograde ejaculation.[15] In rare cases, women will have postoperative dyspareunia that results from unintentional lacerations of the vagina during the

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ABBREVIATIONS USED IN TEXT
IBD = inflammatory bowel disease
TPN = total parenteral nutrition

removal of the rectum. Proctocolectomies in women appear to have a negligible effect on fertility.

Effects of Inflammatory Bowel Disease on Pregnancy

Ulcerative Colitis

Ulcerative colitis does not influence fetal outcome except in severe cases that necessitate surgical intervention. In these, the risk of fetal wastage is high.[16,17] Total parenteral nutrition (TPN) and better fetal monitoring may be improving the prognosis for this group of patients with severe colitis.[17,18] The incidence of spontaneous abortions, stillbirths, prematurity, low-birth-weight infants, and fetal malformations is not increased over the general population. In a recent report, a higher percentage of low-birth-weight infants was found compared with the normal population.[6] This finding, based on the results of only 12 infants, is contrary to that of another recent report of 136 infants of mothers with ulcerative colitis where the incidence of low birth weights was normal (5.4%).[19]

Crohn's Disease

The risk of spontaneous abortion, prematurity, and low-birth-weight infants in patients with Crohn's disease is related to the activity of disease at the time of conception.[7-9] The site of involvement does not appear to affect pregnancy. Surgical intervention for Crohn's disease has resulted in a high degree of fetal wastage.[8] The nutritional support given these women with severe disease was not specified. Recently, normal deliveries in women with severe exacerbations of IBD were the result of long-term maintenance on total parenteral nutrition until delivery.[20-25] A few patients receiving home TPN for their Crohn's disease conceived, maintained, and nursed while on a regimen of TPN.[26,27] One pregnancy managed this way resulted in a child with a partial cleft palate. Whether this was a complication of the therapy or coincidental is not certain.

Effects of Pregnancy on Inflammatory Bowel Disease

Ulcerative Colitis

Pregnancy has not been shown to affect the course of ulcerative colitis. In one recent study involving 97 women with ulcerative colitis,[19] the spontaneous risk of an exacerbation of bowel disease per patient per year in nonpregnant women of child-bearing age was determined to be 32%. When pregnant, the same women's risk rose insignificantly to 34%. Exacerbations of the disease occurred most often in the first and second trimester. In this same series, the three colectomies that were done had no effect on the course of the pregnancy or delivery. Patients who have active disease at the time of conception tend to continue to have the same intensity or an exacerbation of their colitis throughout their pregnancy.[28] Therapeutic abortion has not affected the course of ulcerative colitis in these patients. Thus, although pregnancy is not contraindicated in patients with ulcerative colitis, it is probably best to recommend to patients that they become pregnant when their disease is in a quiescent state. Despite what was initially thought, there is no evidence that an initial attack of colitis during pregnancy is any more severe than that found in nonpregnant patients. Furthermore, the activity of the disease in one pregnancy is probably independent of that which will be experienced during a subsequent pregnancy. Usually flexible sigmoidoscopy provides a relatively safe means to assess the activity of disease in pregnant patients with ulcerative colitis.

Crohn's Disease

Pregnancy does not increase the risk for an exacerbation of Crohn's disease. Nielsen and colleagues found a 44% risk of exacerbation per patient in 59 women who were not pregnant but a 38% risk in the same women when pregnant or after delivery.[23] Patients whose disease was inactive at the time of conception had about a 60% chance of its remaining inactive during the course of their pregnancy. Most patients (more than 50%) who had active disease at the time of conception had either no change or worsening of their disease. While many clinicians have thought that a fairly high percentage of patients will have increased activity of their disease in the postpartum period, Nielsen and co-workers found that postpartum relapses are usually mild and easily managed medically.[23] Mogadam and colleagues found that 23% of 145 women with Crohn's disease had decreased disease activity in the postpartum period, 62% had no change, and 15% had an exacerbation.[28]

Pregnancy and Ileostomy

The investigations into the effect of an ileostomy on pregnancy have mainly involved patients who have had total proctocolectomies for ulcerative colitis and not Crohn's disease. The theoretic possibility exists that the presence of an ileostomy might increase the likelihood of fallopian tube obstruction, lead to dyspareunia, or create psychological difficulties that could interfere with sexual relations. Despite these concerns, ileostomies have not been shown to affect fertility or the course of pregnancy.[19,29,30] Usually pregnancy has little effect on ileostomy function, although the change in shape of the abdomen may require a new appliance.[31] The fluid and electrolyte balance may be more difficult to manage in a nauseated patient with an ileostomy. In one study, 10% of patients with ileostomies had an intestinal obstruction during pregnancy.[30] Increased abdominal pressure may occasionally cause a stomal ileal prolapse. This usually occurs in patients who have had an ileostomy placed less than a year before becoming pregnant.

Similarly, successful term pregnancies have been reported with women who had had a total colectomy with an ileal pouch-anal anastomosis.[32,33] Three of six patients had a transient deterioration of anorectal function during their third trimesters that resolved after delivery.[33]

Medical Therapy for IBD During Pregnancy

Steroids

Corticosteroid administration in pregnant women only rarely results in fetal pituitary adrenal suppression and other fetal complications.[34] This may be due to the placental metabolism of cortisol to the less active cortisone. The concentration of prednisone and prednisolone in a fetus is eight times less than that in the mother. Steroid therapy in pregnant women does not increase the risk of cleft palate as it does in mice. Most studies of the effects of corticosteroid therapy on

pregnancy were done in patients who had diseases other than IBD. Reinisch and associates found a higher percentage of newborns with low birth weights born to mothers who had received 10 mg per day of prednisone during the entire course of their pregnancy compared with a matched control group.[35] Mogadam and co-workers surveyed patients who had IBD and received various drug therapies.[36,37] The use of steroids was found to have no effect on the fetal outcome compared with the general population. Thus, although steroid therapy is not contraindicated during the course of pregnancy and should be used to help control IBD, it should be kept in mind that there is a suggestion in the literature that steroid therapy may cause an increased risk of having a low-birth-weight infant. While adrenal suppression is not common, it should be looked for in infants of mothers who received corticosteroids.

No firm conclusions can yet be made about the effects of steroids on the ability to conceive, on the fetus when administered before conception, and on spermatogenesis.[22] Prednisone and prednisolone pass poorly into milk, and the amount of steroid ingested by a nursing infant is negligible.

Sulfasalazine

Sulfasalazine therapy for IBD during pregnancy has not been associated with fetal wastage, congenital abnormalities, neonatal jaundice, or kernicterus despite various theoretic conjectures based on human experience with other sulfonamides.[38] At birth, the neonatal serum concentration of sulfasalazine is comparable to that in the mother. The elimination of the drug by neonates is slower than by adults.[39] A negligible amount of sulfasalazine is found in the milk of lactating women taking therapeutic amounts of the drug, but the concentration of sulfapyridine, the major sulfa metabolite of sulfasalazine, is 45% that in maternal serum.[1,39] Neither sulfasalazine nor sulfapyridine displace bilirubin from its albumin binding sites, and, therefore, their use does not increase the incidence of neonatal jaundice or kernicterus in neonates.[40] As with steroid therapy, sulfasalazine therapy should be continued throughout pregnancy and after delivery if medically indicated to control IBD. A favorable outcome of pregnancy appears to depend on keeping IBD in remission and thus takes precedence over theoretic considerations about the effects of steroid and sulfasalazine therapy on the fetus. The effects of sulfasalazine use on male fertility have been alluded to earlier.

Mercaptopurine, Azathioprine, and Metronidazole

Mercaptopurine and azathioprine should not be administered during pregnancy as their safety is not yet established. Animal models have shown that these immunosuppressives may cause severe disorders in fetuses including lymphopenia, thymic hypoplasia, immunoglobulin deficiency, low cortisol levels, and chromosomal abnormalities. Patients with IBD who are taking these drugs should be weaned from them before becoming pregnant. Some clinicians have recommended a therapeutic abortion for patients who become pregnant while receiving these drugs,[22] based on an uncertainty about the effects on human fetuses. More than 1,000 renal transplant recipients have had successful pregnancies despite immunosuppressive therapy.[41] Of 103 births in women with renal transplants who were taking azathioprine, 7 infants had birth defects. The mothers taking higher doses of azathioprine had a higher incidence of infants with these anomalies.[42] The time interval between discontinuing the drug and becoming pregnant required to reduce the drugs' toxic effects is not known. Terminating the pregnancy based on the mother's previous and concurrent use of azathioprine and mercaptopurine must therefore be considered elective and not mandatory.

Metronidazole is mutagenic to bacteria on the Ames assay and at high doses is tumorigenic to rats, but the drug has not been teratogenic to other animals or humans. Because of the concern about theoretic teratogenicity, manufacturers recommend that the drug not be used during the first trimester of pregnancy. Metronidazole can therefore be used to control IBD in the second and third trimesters of pregnancy, if it is clinically indicated.[43]

Conclusion

For the most part, inflammatory bowel disease and pregnancy appear to be independent processes. Because the nutritional needs of patients increase during pregnancy and during flares of the disease, astute nutritional management is essential for a successful outcome of pregnancy. Pregnant patients with active disease fare worse than those with inactive disease. There is little evidence that pregnancy affects the course of IBD. Conversely, ulcerative colitis does not affect pregnancy except in severe cases, and some studies suggest that Crohn's disease in mothers may predispose the neonates to low birth weights. Sulfasalazine and steroid regimens are effective in controlling IBD during pregnancy and should not be withdrawn in a pregnant patient who requires them to maintain or achieve a quiescent state of disease. Immunosuppressive therapy should be avoided, but the use of such drugs is not an absolute indication for terminating a pregnancy. A team approach to pregnancy in a woman with inflammatory bowel disease with a gastroenterologist, surgeon, and perinatologist has increased the likelihood of a successful outcome. A woman of child-bearing age with IBD should not be discouraged from becoming pregnant if her disease is quiescent or mild. Contraception may have a place if the disease is moderate to severe and the likelihood of surgical intervention is imminent.

The most succinct and well-written summary of IBD and pregnancy for both physicians and patients is a pamphlet, "Questions and Answers About Pregnancy in Ileitis and Colitis," distributed free by the National Foundation for Ileitis and Colitis, 295 Madison Avenue, New York, NY 10017 (telephone 212-685-3440). Other medical reviews of this subject are by Vender and Spiro,[22] Warsof,[44] Sorokin and Levine,[45] Korelitz,[46] Fielding,[47] Donaldson,[48] Hanan and Kirsner,[49] and Miller.[50]

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Specialty Conference

Common Causes of Cardiac Emboli—Left Ventricular Thrombi and Atrial Fibrillation

Discussant
JOHN R. STRATTON, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

JOHN R. STRATTON, MD*: Emboli from cardiac sources can lodge in the brain or the periphery. Embolism to the periphery, such as to the kidneys, spleen, or extremities, is frequently clinically silent, but embolism to the brain is usually symptomatic. Therefore, the distribution of clinically detected emboli is roughly three-quarters cerebral and one-quarter peripheral. Cardiac emboli are a relatively common cause of stroke syndromes, accounting for about 13% of all strokes, with about two thirds of these embolic events leading to serious morbidity or death.[1,2]

The sources of cardiogenic emboli are listed in Table 1. Rheumatic mitral valve disease was previously the leading source of cardiogenic embolism but is now an infrequent cause. Currently about 45% of all cardiogenic emboli are associated with nonvalvular atrial fibrillation, and 25% are associated with acute or chronic myocardial infarction.[1] Most emboli in patients with atrial fibrillation are due to left atrial thrombi, and most emboli in patients with ischemic heart disease arise from left ventricular thrombi. The remaining 20% of cardiac emboli are due to prosthetic heart valves, nonbacterial thrombotic endocarditis, bacterial endocarditis, mitral prolapse, tumors, idiopathic cardiomyopathy, and other rarer disorders.

There has been a recent proliferation of useful information concerning the two leading causes of cardiogenic emboli, atrial fibrillation and left ventricular thrombus. Left ventricular thrombus has been recognized as a clinically important disorder only in the current decade, with the development of imaging modalities capable of detecting a thrombus during life. In addition, the importance of nonvalvular atrial fibrillation as a cause of stroke has only recently been appreciated. In the rest of this discussion I will focus on these two common causes of cardiogenic emboli and will review the recommended anticoagulant therapy after an embolic event has occurred.

Left Ventricular Thrombi

Diagnosis of Left Ventricular Thrombi

Until recently, the accurate diagnosis of a left ventricular thrombus was possible only at the time of autopsy. Left ventricular thrombus was suggested clinically if a systemic embolus occurred but, even when suspected, could not be proved during life.

Several imaging techniques are capable of detecting left ventricular thrombi (Table 2). With the exception of radionuclide imaging using platelets labeled with indium 111, all of the listed techniques detect a space-occupying lesion within the left ventricle. Both invasive contrast angiography[3-5] as done at the time of cardiac catheterization and radionuclide angiography[4-6] detect thrombi as areas of negative or absent contrast; the sensitivity of these two techniques is low, in the range of 31% to 62%. X-ray computed tomographic (CT) scanning[7,8] and magnetic resonance imaging[9] are both capable of generating images of left ventricular thrombi, but the diagnostic accuracy of these techniques has not been defined. Furthermore, these techniques are expensive and not widely available.

Indium 111 platelet imaging provides information about left ventricular thrombi that is not available with other techniques.[10,14,15] With this technique, autologous platelets are labeled and reinjected into the patient. Serial imaging is then carried out over a period of four to five days (Figure 1). The half-life of the isotope is three days, which allows repeat imaging for as long as a week. Left ventricular (LV) thrombi are detected as localized areas of uptake in the left ventricle. Because this technique can estimate thrombus activity, it provides unique information about LV thrombi. For example, ^{111}In-platelet imaging has shown that most thrombi have continuing platelet uptake regardless of the age of the thrombus.[10,14,15] Thrombi that have been excised at the time of an operation following platelet labeling have radioactivity ratios of approximately 10:1 to 355:1 compared with whole blood, indicating active platelet deposition on the thrombus surface.[10,11] The sensitivity of platelet imaging for detecting LV thrombi is 71%, and the specificity is 100%.[11]

In contrast to the information about thrombus activity obtained by platelet imaging, echocardiography gives information about the anatomic location, size, and morphologic features of thrombi. A study done at the University of Washington found a sensitivity of 86% and a specificity of 95%,[11] and subsequent studies have confirmed these findings.[4,5,12,13]

Echocardiography, however, does have several limita-

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
INR = international normalized ratio
LV = left ventricular

tions for the diagnosis of left ventricular thrombus. About 5% to 10% of studies are technically poor and cannot adequately exclude the presence of a thrombus. Anatomic structures such as trabeculations, aberrant bands, papillary muscles, and tumors are occasionally mistaken for LV thrombi and cause falsely abnormal ("false-positive") studies.[11,16,17] In addition, echocardiographic artifacts due to noise or resolution problems cause false-positive studies.[11,18] Nevertheless, because of its wide availability, relative inexpensiveness, and lack of radiation exposure, echocardiography is the method of choice for diagnosing left ventricular thrombus. When technically inadequate studies occur or concern exists about a potentially false-positive study, other more expensive diagnostic techniques such as platelet imaging or contrast-enhanced x-ray CT are alternatives.

Left Ventricular Thrombi in Acute Myocardial Infarction

Prevalence and time of formation. Substantial evidence indicates that LV thrombi occur almost exclusively in association with anterior myocardial infarctions (Table 3). They develop in about a third of patients who have anterior transmural myocardial infarctions. In contrast, their occurrence in patients with inferior transmural infarctions or with non-Q wave infarction is rare.[19-24] The predominant development of left ventricular thrombi in anterior wall infarctions in contrast to other types of infarction is partially explained by several factors. Apical akinesis, or dyskinesis, appears to be a nearly uniform prerequisite for the development of a thrombus, and apical wall motion abnormalities are much more common with anterior infarctions than with other infarctions. In addition, anterior infarctions are larger than inferior infarctions, which predispose both to a stasis of blood and to an increased release of substances that promote local thrombus formation. Anterior infarctions are also more commonly associated with aneurysm formation with resultant blood stasis than are other types of infarctions. One study has suggested that left ventricular thrombus formation is increased in patients with transmural anterior infarctions treated with the β-blocker timolol maleate, possibly because of greater apical wall motion abnormalities.[25]

The time of left ventricular thrombus formation following infarction has been described in several studies in which serial echocardiograms were done.[20-22,24,33,34] Few thrombi (0% to 14%) are present within 24 hours of the onset of infarction. Within 48 hours of infarction, only 46% to 55% of thrombi are present, but within a week of infarction, nearly all thrombi (83% to 100%) have formed. In one study,

TABLE 1.—*Cardiac Sources of Embolic Stroke*

Cardiac Disease	*Approximate Percentage of All Embolic Strokes, %*
Ischemic heart disease—acute or chronic infarction	25
Nonvalvular atrial fibrillation	45
Valvular heart disease	10
Prosthetic heart valves	10
Other—prolapse, endocarditis, tumors, paradoxic emboli, cardiomyopathy	10
	100

TABLE 2.—*Diagnostic Techniques for Detecting Left Ventricular Thrombi*

Diagnostic Technique	*Sensitivity, %*	*Specificity, %*
Two-dimensional echocardiography*	77-95	88-100
Indium 111 platelet imaging†	71	100
Radionuclide angiography‡	31-62	92-100
Contrast angiography§	31-62	75-100
X-ray computed tomography‖	....	....
Magnetic resonance imaging¶	....	....

*From Pechacek et al,[4] Starling et al,[5] Ezekowitz et al,[10] Stratton et al,[11] Visser et al,[12] and Lupi et al.[13]
†From Stratton et al,[13] Stratton et al,[14] and Bellotti et al.[15]
‡From Pechacek et al,[4] Starling et al,[5] and Stratton et al.[6]
§From Reeder et al,[3] Pechacek et al,[4] and Starling et al.[5]
‖From Tomoda et al[7] and Nair et al.[8]
¶From Higgins et al.[9]

24 hours 96 hours

Figure 1.—Anterior views of imaging using platelets labeled with indium 111—300,000 counts per view—were taken at 24 and 96 hours following the ^{111}In-platelet injection. The localized platelet uptake **(arrows)** denotes a left ventricular thrombus. The images are more pronounced at 96 hours than at 24 hours owing to the continued accretion of labeled platelets onto the thrombus and to a reduction in circulating background blood pool activity. The liver is at the lower left and the spleen at the lower right of both images.

TABLE 3.—*Risk of Systemic Embolization If Left Ventricular Thrombus Present in Acute Myocardial Infarction*

Source	Patients With Thrombi, No.	Patients Receiving Anti-coagulants,* No.	Mean Follow-up, mo	Emboli Before or After Echo†
Asinger et al, 1981[20]	12	7	7	0/12 (0)
Friedman et al, 1982[26]	11	9	11	2/11 (18)
Keating et al, 1983[27]	17	10	8	6/17 (35)
Haugland et al, 1984[28]	31	NA	10	9/31 (29)
Johannessen et al, 1985[23]	15	15	0.5	4/15 (27)
Visser et al, 1984[22]	22	22	12	1/22 (4)
Weinreich et al, 1984[19]	43	18	10	7/43 (16)
Spirito et al, 1985[21]	24	0	7	1/24 (4)
Visser et al, 1985[29]	46	NA	NA	12/46 (26)
Tramarin et al, 1986[30]	34	17	12	1/34 (3)
Domenicucci et al, 1987[24]	59	0	14	5/59 (8)
Johannessen et al, 1988[31]	55	55	3	15/55 (27)
Turpie et al, 1988[32]	33	8	0.4	3/33 (9)
Overall	402	161		66/402 (16)

echo=echocardiogram, NA=not available

*Heparin or sodium warfarin were used in anticoagulation therapy.

†The numbers represent the number of systemic embolic events versus the number of patients with left ventricular thrombi (%).

12% formed later than two weeks.[24] The mean time to thrombus formation was about 5 days in one study[20] and 12 days in another.[24] Thus, an echocardiogram done within the first several days of infarction cannot exclude the possibility of later thrombus development. Because of the relatively wide variability in the time of thrombus formation and the probable efficacy of early anticoagulation in preventing thrombus formation, it is unreasonable to adopt a treatment strategy that requires the echocardiographic diagnosis of a thrombus before instituting anticoagulant therapy.

Embolic risk of left ventricular thrombi in acute infarction. The presence of a left ventricular thrombus is associated with a considerable risk of systemic embolization. In the largest available study of 150 patients with a first anterior wall infarct, 27% of the patients in whom LV thrombi developed suffered systemic emboli within three months.[23] In contrast, only 2% of patients with anterior infarction in whom LV thrombi did not develop suffered systemic emboli. Although most large studies have shown a substantial embolic risk—and the risk pooled from all studies is about 16%—as shown in Table 3, agreement has not been uniform that LV thrombi are associated with such an increased risk. The range of reported embolic events in studies of patients with echocardiographically detected thrombi has varied between 0% and 35%.[19-24,26-32] The discrepancies are difficult to reconcile but may be due in part to retrospective versus prospective data collection, differences in diagnostic criteria for thrombus or embolus, differences in anticoagulant therapy, and other baseline differences in patient populations.

Predictors of embolization. No clinical features strongly predict embolization in a patient with a left ventricular thrombus. Two echocardiographic features, however, thrombus protrusion and thrombus mobility, may be of some use for predicting the risk of embolization.[28,29,31,35] Of all thrombi, 34% to 55% protrude into the ventricular cavity, and the rest are flat; protruding thrombi are associated with embolization in 22% to 56% of cases, but flat thrombi are associated with embolization in only 3% to 13% of cases. Thrombus mobility, defined as the movement of a thrombus independent of the underlying myocardium, occurs in 15% to 27% of thrombi, and the remainder of thrombi are immobile; between 35% and 83% of patients with a mobile thrombus suffer systemic embolization compared with only 5% to 16% of patients with immobile thrombi.

Although those features are of some use in predicting the embolic risk, spontaneous changes in these features are common in patients with acute myocardial infarction. Domenicucci and co-workers noted that 41% of patients had changes in thrombus shape and 29% had changes in thrombus mobility over a 14-month follow-up after an acute infarction.[24] In contrast, among 48 patients with chronic myocardial infarction or cardiomyopathy, we noted changes in thrombus shape in only 16% and changes in thrombus mobility in only 10% over a two-year follow-up.[36]

Among 58 patients with LV thrombi diagnosed by echocardiography, we noted a higher embolic rate in patients who also had a positive ^{111}In-platelet image (23%, 7 of 30) compared with patients with a negative platelet image (4%, 1 of 28) during a 38-month follow-up.[37] Thus, thrombosis imaging may stratify the embolic risk in patients with left ventricular thrombi diagnosed by echocardiography.

Preventing left ventricular thrombi with early anticoagulation. In two older studies of anticoagulation in patients with acute infarction, the autopsy prevalence of LV thrombi was reported in a total of 112 patients who were randomly assigned to receive either early or no anticoagulation. Among non-anticoagulated patients, 49% had a left ventricular thrombus at autopsy compared with only 19% of patients who were anticoagulated.[38,39] These data suggested that early anticoagulation in myocardial infarction reduces the prevalence of left ventricular thrombi.

Using echocardiographic detection of LV thrombi as the end point, the role of early heparin and sodium warfarin therapy in preventing left ventricular thrombi was examined in five recent randomized clinical trials (Table 4).[32-34,40,41] In all series, full-dose heparin therapy was used and serial echocardiograms were done. The trials varied in the dose of heparin and the therapy, if any, for the control group. The results from these studies, completed in Australia,[34] France,[33] Norway,[40] Canada,[32] and the United States,[41] are conflicting. The study by Davis and Ireland reported no apparent benefit, but both the anticoagulated and control groups had an unusually high prevalence of thrombus formation (56%).[34] The study by Arvan and Boscha found no benefit, but only 30 patients were included.[41] The study by Gueret and associates reported a trend toward a reduction in LV thrombi from 52% to 38% among patients receiving early heparin therapy compared with controls, but this was not statistically significant.[33] In the Norwegian trial, a thrombus developed in 21% of control patients compared with 0% of the patients treated with heparin therapy ($P < .05$).[40]

The largest study, by Turpie and colleagues, randomly assigned patients with a first anterior myocardial infarction to receive either fixed full-dose heparin, 12,500 units twice a day, or to low-dose heparin, 5,000 units twice a day; the high-dose group had a significant reduction in LV thrombus formation at ten days compared with controls (9% versus 31%, $P < .01$).[32] Many of the patients in whom LV thrombi developed despite high-dose heparin therapy had subtherapeutic heparin levels, suggesting that titrating the dose may be better than a fixed dosing schedule. Thus, the available data, although somewhat conflicting, suggest that early full-

TABLE 4.—*Randomized Trials of Full-Dose Anticoagulation to Prevent Left Ventricular (LV) Thrombi in Acute Myocardial Infarction*

Source	Patients, No.	Hours to Randomization or Treatment	Anticoagulant Regimen‡	Control Regimen	Time of Last Echo, days	LV Thrombi Treated, %	LV Thrombi Control, %	LV Thrombi P Value
Nordrehaug et al, 1985[40]	53	4.6±2.5†	Heparin, warfarin	Placebo	10	0	21	<.05
Davis and Ireland, 1986[34]	52	<12*	Heparin, warfarin	Low-dose heparin; warfarin if creatine kinase >1,000 U/liter	7-14	56	56	NS
Gueret et al, 1986[33]	46§	5.2±4.6*	Heparin	No therapy	20-50	38	52	NS
Arvan and Boscha, 1987[41]	30	6.5±3.3†	Heparin, warfarin	No therapy	14	31	35	NS
Turpie et al, 1988[32]	167	<36*	Heparin, 12,500 b.i.d.	Heparin, 5,000 b.i.d.	10	9	31	<.01
Total	348							

b.i.d.=twice a day, echo=echocardiogram, NS=not significant

*Hours to randomization.
†Hours to treatment.
‡All studies except Turpie et al used adjusted-dose anticoagulants.
§This study included only patients with anterior wall myocardial infarctions.

TABLE 5.—*Systemic Emboli in Patients With Acute Myocardial Infarction Receiving Anticoagulation Versus Control Regimen: Data From Randomized Trials for Left Ventricular (LV) Thrombus Prevention**

Source	Follow-up Duration, mo	Systemic Embolic Events: Patients Receiving Full-Dose Anticoagulants	Systemic Embolic Events: Patients on Control Regimen
Nordrehaug et al, 1985[40]	~0.5	0/26	1/27
Davis and Ireland, 1986[34]	~0.5	0/27	1/25
Gueret et al, 1986[33]	0.6-1.7	1/21	1/25
Arvan and Boscha, 1987[41]	1	1/17	1/13
Turpie et al, 1988[32]	~0.5	1/83	3/84
Overall		3/174 (1.7%)	7/174 (4.0%)

*These data refer to all treated and control patients, whether or not an LV thrombus developed.

dose anticoagulation reduces LV thrombus formation in cases of acute anterior infarction.

No studies to date have shown any benefit of platelet inhibitory agents in decreasing left ventricular thrombus formation. In one randomized trial of 100 patients with acute myocardial infarction, Funke Küpper and co-workers found no reduction in LV thrombus formation using sulfinpyrazone plus oral anticoagulants compared with using oral anticoagulants only (20% in both groups).[42] In a subsequent randomized study in 100 patients, they found that the use of aspirin, 100 mg a day, did not result in a reduction in LV thrombus formation compared with placebo (33% in both groups).[43] In a randomized trial of patients with a first anterior wall myocardial infarction, we found no reduction in LV thrombus formation in patients treated with aspirin plus dipyridamole compared with placebo-treated patients.[44] Two studies have suggested that intracoronary streptokinase does not reduce LV thrombus formation,[45,46] whereas one small nonrandomized uncontrolled trial suggested that administering intravenous streptokinase did reduce LV thrombus formation.[47]

Reduction in embolic events with early anticoagulation. In addition to the probable effectiveness of acute anticoagulation for reducing thrombus formation, substantial evidence suggests that early anticoagulation more importantly reduces the risk of stroke. In three large older randomized trials of anticoagulation in acute myocardial infarction, a total of 3,562 patients in whom the presence or absence of left ventricular thrombi was unknown were studied.[38,39,48,49] In each study, there was a reduction in systemic emboli, which was 55% for one trial ($P<.01$),[48] 24% for another (P=NS),[39] and 75% for a third ($P<.01$).[38] Approximately 2% to 6% of patients in the control groups had embolic events, compared with only 1% to 2% of patients in the anticoagulated groups. In all three trials, the bleeding risk was higher in the anticoagulated groups, as would be expected. Bleeding occurred in 5% to 13% of patients receiving anticoagulants but in only 1% to 5% of controls.[50] There were no cases of fatal bleeding in any of the trials, however. Thus, anticoagulation of all patients with an acute myocardial infarction reduces systemic emboli but exposes some patients with a low embolic risk to possible bleeding complications. Given our current knowledge that left ventricular thrombi develop in patients with anterior myocardial infarctions, therapy can be targeted to this high-risk group.

At present, there are relatively few data concerning the efficacy of early anticoagulation in reducing the risk of systemic emboli. The recent randomized trials of anticoagulation for LV thrombus prevention were too small and had too short a follow-up to definitively assess embolism as an end point. Nevertheless, when all studies were pooled, there was a trend for a reduction in embolic events from 4.0% (7 of 174) in control patients to 1.7% (3 of 174) in patients receiving anticoagulation during a brief follow-up (Table 5).[32-34,40,41]

The potential effects of anticoagulant therapy in patients in whom LV thrombi have developed are summarized in Table 6. Only studies that reported on both anticoagulated and non-anticoagulated patients are included. Overall, there is a trend for a reduction in embolic events among patients with LV thrombi treated with full-dose anticoagulation compared with untreated patients with LV thrombi (5% versus 18%).[19,20,26,27,30,32-34,41]

Recommendations for anticoagulation in acute myocardial infarction. Patients who have an anterior transmural myocardial infarction should receive full-dose heparin therapy followed by warfarin therapy for three months to prolong the prothrombin time to an international normalized ratio (INR) of 2.0 to 3.0—which corresponds to a prothrombin time of 1.2 to 1.5 times a control time using a rabbit brain thromboplastin reagent.[49,51] Therapy should be instituted as early as possible, based on a history and electrocardiogram suggestive of acute anterior infarction, because early therapy reduced thrombus development. This regimen, in addition to preventing the development of thrombi in many

TABLE 6.—*Systemic Emboli in Patients in Whom Left Ventricular Thrombi Develop in Acute Infarction: Possible Efficacy of Anticoagulant Therapy*

Source	Duration of Follow-up, mo	Systemic Embolic Events* Full-Dose Anticoagulants		No Full-Dose Anticoagulants	
Asinger et al, 1981[20]	7	0/5	(0)	0/7	(0)
Friedman et al, 1982[26]	11	1/9	(11)	1/2	(50)
Keating et al, 1983[27]	11	0/10	(0)	6/7	(86)
Weinreich et al, 1984[19]	15	0/25	(0)	7/18	(39)
Davis and Ireland, 1986[34]	<1	0/14	(0)	1/15	(7)
Gueret et al, 1986[33]	0.6-1.7	1/8	(12)	1/13	(8)
Tramarin et al, 1986[30]	12	1/17	(6)	0/17	(0)
Arvan and Boscha, 1987[41]	<1	1/4	(25)	1/6	(17)
Turpie et al, 1988[32]	<1	1/8	(12)	3/25	(12)
Overall		5/100	(5)	20/110	(18)

*The numbers represent the number of embolic events versus the number of patients in each group with left ventricular thrombi (%).

patients, enhances the resolution of formed thrombi. Most important, the risk of embolization is reduced.

In patients with inferior wall myocardial infarctions or nontransmural infarctions, low-dose heparin therapy, 5,000 units intravenously or subcutaneously every 12 hours, should be given until a patient is fully ambulatory to prevent venous thromboembolism.[49] In addition, some authors recommend that patients with inferior wall or nontransmural infarctions who are at an increased risk of systemic embolism because of atrial fibrillation, congestive heart failure, or a history of systemic or pulmonary embolus also receive the same heparin-warfarin regimen as patients with anterior transmural infarctions. The evidence of benefit in these patient groups is limited, however. All subjects should receive aspirin, 325 mg initially, and 325 mg per day subsequently unless a contraindication to using aspirin is present.[49]

These recommendations do not require the use of echocardiography but rely solely on electrocardiographic criteria. Waiting for an echocardiogram to show a left ventricular thrombus misses the opportunity to prevent thrombus formation and can lead to unnecessary echocardiograms.

Many patients, particularly those with anterior wall infarctions, now receive early thrombolytic therapy with tissue plasminogen activator or streptokinase. Because the available data suggest that thrombolytic therapy does not reduce the risk of left ventricular thrombus formation, it is probably reasonable to apply the same anticoagulant guidelines noted above to patients following thrombolytic therapy, although the use of heparin following intravenous streptokinase was associated with increased bleeding in the Second International Study of Infarct Survival.[52] Whether early angioplasty reduces the risk of left ventricular thrombus development and therefore the risk of embolization is unknown. Currently it is probably prudent to follow the same guidelines for anticoagulation noted earlier in patients with anterior wall infarctions who have early angioplasty. Additional studies are clearly needed to clarify the role of heparin and warfarin therapy, with or without platelet inhibitor therapy, in patients treated with thrombolytic agents or angioplasty.

Embolic Risk of Chronic Left Ventricular Thrombi

Much less is known about the fate and embolic potential of left ventricular thrombi that are present months to years following myocardial infarctions or in patients with idiopathic cardiomyopathy. Persistent left ventricular thrombi are common following a myocardial infarction. Approximately 24% of patients dying with a healed infarct have a left ventricular thrombus compared with 37% of patients dying with an acute infarction.[53] The recognized prevalence among living patients with remote infarction, however, is lower—about 10% to 14%. The relatively high prevalence of chronic thrombi can be attributed to the low rate of the spontaneous resolution of thrombi. In recent studies, only about a quarter of untreated patients with left ventricular thrombi had thrombus resolution over a 3- to 12-month period.[21,54] Therefore, thrombus resolution is uncommon without therapy.

Retrospective studies have suggested a substantial embolic risk—7% to 19%—due to chronic left ventricular thrombosis.[29,31,55] To define prospectively the embolic risk, 85 patients with LV thrombi predominantly due to remote myocardial infarction were observed at the University of Washington.[35] A control group was also observed because of the diagnostic uncertainty concerning the etiology of central nervous system events in a population of patients with diffuse atherosclerosis. The control group consisted of 91 patients who did not have LV thrombi but who were otherwise similar to the patients who did. The mean follow-up was 22 months, and emboli were strictly defined by criteria recently developed by Hart and associates.[56] Both groups had a low ejection fraction; the mean time from the last infarction was 32 months in the LV thrombus group and 48 months in the control group.

During follow-up, 13% of subjects with LV thrombi had embolic events compared with 2% of control subjects ($P<.01$). By life-table methods, at two years of follow-up 97% of control subjects were embolus-free compared with 86% of patients with thrombi ($P<.01$).[35] These data document that patients with LV thrombi present at times remote from an acute myocardial infarction are at an increased risk for systemic embolization.

The correct anticoagulant therapy, if any, for patients with chronic left ventricular thrombi remains unknown. The recent National Heart, Lung, and Blood Institute's National Conference on Antithrombotic Therapy offered no recommendations for the management of patients with chronic thrombi. In a small number of patients with chronic thrombi, we have shown that the use of the combination of aspirin plus dipyridamole or sulfinpyrazone alone inhibits platelet uptake, as shown by platelet imaging in some patients with chronic left ventricular thrombi. Warfarin therapy also resolved thrombi in some cases and may lead to decreased thrombus activity in other cases.[57]

In our study, warfarin therapy was at the discretion of the individual physician. Among 23 warfarin-treated patients, 2 (9%) had emboli, but both emboli occurred within the first five days of therapy; among 62 nontreated patients, 9 (14%) had emboli. Warfarin therapy, however, was associated with bleeding complications in 20% of treated patients observed for a mean of 13 months.[35]

The risks associated with long-term warfarin administration have been comparable in other much larger trials in patients with ischemic heart disease, with an overall pooled bleeding risk of 23%, a major bleeding risk of 4.7%, and a fatal bleeding risk of 1.0% in patients who were on long-term anticoagulation.[50] Because the bleeding risk of long-term full-dose anticoagulation may outweigh the risk of

embolism, the proper therapy for patients with chronic left ventricular thrombus is unclear. Two alternatives with a potentially lower risk are lower intensity warfarin therapy and platelet-inhibitory agents, but neither approach has been tested prospectively to determine if it would reduce the embolic rate. The current practice at the University of Washington is to not treat patients who have chronic thrombi with a full-dose warfarin regimen unless they have suffered a previous embolus or unless echocardiographic features (thrombus protrusion and motility) suggest a high risk of embolization.

Left Ventricular Thrombi and Left Ventricular Aneurysms

About half of all patients with chronic left ventricular aneurysms have associated left ventricular thrombi. Retrospective studies have suggested, however, that the risk of embolization in patients with left ventricular aneurysms is low despite the high prevalence of left ventricular thrombus. The prevalence of embolization found in three retrospective reviews was only 1% to 5%.[3,58,59] The studies may have been biased against including patients with emboli because participating patients had to be fit enough to undergo cardiac catheterization, surgical treatment, or both. Recent echocardiographic data from Haugland and colleagues and from the University of Washington suggest that the presence of an associated aneurysm does not reduce the risk of embolization.[28,35] In our prospective study, emboli occurred in 13% of patients with thrombi and aneurysm, compared with 14% of patients with thrombi and no aneurysm.

Atrial Fibrillation and Embolic Risk

Systemic Embolism in Rheumatic Heart Disease

Among all patients with rheumatic mitral valvular disease, the lifetime risk of systemic embolization if atrial fibrillation is present is substantially increased, with a minimum estimate being 20%.[60] The risk of systemic embolism with atrial fibrillation is at least four times that with sinus rhythm.[60,61] Overall, the embolic rate was 5.2% per year for patients who were in atrial fibrillation in one study compared with 0.7% for patients in normal sinus rhythm.[62] This increased risk exists both for patients with rheumatic mitral stenosis and for patients with mitral regurgitation.[63]

In patients with rheumatic heart disease, about 82% of all emboli occur while the patient is in atrial fibrillation.[60] The overall prevalence of emboli is 7% in patients with sinus rhythm but 30% in patients with atrial fibrillation.[61] Left atrial thrombus appears to be the source for most of these emboli, as indicated by data showing that about 41% of patients with rheumatic atrial fibrillation have associated left atrial thrombi compared with only 9% of patients in normal sinus rhythm.[60] Fully 87% of patients with atrial thrombi are in atrial fibrillation. Approximately 41% of patients with left atrial thrombi have emboli compared with 16% or less of patients without left atrial thrombi.[60]

Several studies suggest a considerable reduction in the systemic embolic rate with anticoagulation in patients with rheumatic mitral valve disease and atrial fibrillation who have already suffered an embolus.[60-65] There are no controlled trials of anticoagulation of patients who have not yet had an embolus. In an observational study by Szekely, warfarin-treated patients had an embolic rate of 4.2 per 100 patient-years compared with 6.8 in non-anticoagulated patients.[62]

Because of the established high risk of emboli in patients with rheumatic heart disease who have chronic atrial fibrillation, the current recommendation is to anticoagulate all patients in this group at a low intensity (INR of 2.0 to 3.0).[59] All patients with systemic emboli, regardless of their current rhythm, should be anticoagulated at a high intensity (INR of 3.0 to 4.5).[1,59] There is much less agreement concerning the anticoagulation of patients with rheumatic heart disease who are in normal sinus rhythm. Some groups have suggested that patients in normal sinus rhythm with severe left ventricular dysfunction, a large atrium, or a left atrial clot should receive long-term anticoagulation.

Embolization in Nonvalvular Atrial Fibrillation

Nonvalvular atrial fibrillation is a recently adopted term for an old disease. As a diagnostic category, it encompasses all patients with atrial fibrillation except those with substantial mitral stenosis or regurgitation. Nonvalvular atrial fibrillation is largely a disease of aging and develops in about 5% of people older than 65 years.[66] Other conditions associated with nonvalvular atrial fibrillation include ischemic heart disease, thyrotoxicosis, hypertension, dilated cardiomyopathy, and hypertrophic cardiomyopathy. Although at least one of these conditions will occur in most people with nonvalvular atrial fibrillation, about 10% to 15% of patients will have so-called idiopathic or "lone" atrial fibrillation without another associated disease.

Nonvalvular atrial fibrillation is important because it is a risk factor for stroke.[1,61] An early indication that nonvalvular atrial fibrillation was not a benign disorder came from an autopsy study that showed a 30% prevalence of embolization in patients with nonvalvular atrial fibrillation, which was similar to the 40% prevalence of embolization in patients with rheumatic mitral valve disease. The embolic prevalence was only 7% in control patients with normal sinus rhythm.[67]

The current knowledge about the stroke risk due to nonvalvular atrial fibrillation has been derived largely from the Framingham study in which 5,191 patients were observed.[66,68-70] Nonvalvular atrial fibrillation increased the risk of stroke fivefold.[68,69] The annual risk of stroke was about 5% per year, and the lifetime risk of stroke was about 30%. Moreover, the risk of recurrence after a first stroke with nonvalvular atrial fibrillation was high. The increased risk of stroke was independent of associated cardiac failure, coronary heart disease, and hypertension. The contribution of atrial fibrillation to the risk of stroke was at least as powerful as other common risk factors including age, systolic blood pressure, congestive heart failure, and coronary artery disease. The risk of stroke associated with nonvalvular atrial fibrillation appeared to increase with age. Only 9% of stroke patients in the 55- to 64-years age group had associated atrial fibrillation, whereas 40% of stroke patients older than 85 years had associated atrial fibrillation.

The importance of atrial fibrillation as a risk factor for stroke was noted in the subset of the Framingham population that had lone or pure atrial fibrillation unassociated with other diseases that predispose to stroke.[70] Of all patients with atrial fibrillation in the Framingham study, 11% had lone or pure atrial fibrillation; with lone atrial fibrillation, the risk of stroke was four times greater than for control patients.[70] Overall, 27% of the patients with lone atrial fibrillation had strokes.

A recent study from the Mayo Clinic, however, reported a low risk of stroke in patients with lone atrial fibrillation. Among all patients with atrial fibrillation, 97 (2.7%) were classified as having lone atrial fibrillation. The criteria for lone atrial fibrillation were age younger than 60, no hypertension, ischemic heart disease, congestive heart failure, any mitral valve disease, and no lung disease. Most of these patients had paroxysmal atrial fibrillation; only 22% had chronic atrial fibrillation. In this highly selected group, only 4 (4%) had embolic strokes over a 15-year follow-up.[71]

There is no consensus as to whether anticoagulation should be prescribed for patients with nonvalvular atrial fibrillation.[61] In practice, warfarin is rarely used because of the known bleeding risk. In addition, the relatively substantial risk of stroke has only recently been appreciated. In a recently reported trial, however, a benefit of warfarin therapy is strongly suggested. In this trial, 1,007 patients with nonrheumatic atrial fibrillation were randomly assigned to receive either high-intensity warfarin (INR of 2.8 to 4.2; $n = 335$), aspirin (75 mg daily; $n = 336$), or a placebo ($n = 336$).[72] The incidence of thromboembolic complications—stroke, transient ischemic attack, or peripheral emboli—and vascular death was reduced with warfarin therapy but not with aspirin. The yearly incidence of thromboembolic complications was 2.0% with the use of warfarin and 5.5% with aspirin and with placebo. There were more nonfatal bleeding episodes with warfarin therapy ($n = 21$) than with the use of aspirin ($n = 2$) or placebo ($n = 0$), but only one fatal bleeding episode. Several additional randomized studies, which are assessing less intense warfarin therapy, are currently underway.

Anticoagulation for Elective Cardioversion of Atrial Fibrillation

The most comprehensive data regarding the risk of embolization following elective cardioversion was reported from a nonrandomized study in Sweden.[73] Bjerkelund and Orning showed a substantially lower risk of systemic embolization following cardioversion among patients receiving anticoagulation compared with patients not receiving anticoagulation (0.8% versus 5.3%).[73] In the subset of patients with nonvalvular atrial fibrillation, the prevalence of emboli was reduced from 7.8% to 1.3%. The current recommendation is to anticoagulate patients for three weeks before elective cardioversion and for an additional four weeks after cardioversion at a low intensity (INR of 2.0 to 3.0).[61] For atrial fibrillation of a short duration—less than three days—and for patients with atrial flutter or supraventricular tachycardia, anticoagulation is not recommended.[61]

Anticoagulation Following Cerebral Embolism

There are many causes of ischemic stroke syndromes. In a given patient, it is often difficult to determine whether a stroke is caused by a cardiogenic embolus, cerebrovascular atherosclerosis, or another disorder. The clinical differentiation based on history, physical examination, and diagnostic test results has recently been outlined by Sherman and coworkers.[1,2] Of patients with a known potential cardiac source of embolization (most commonly left ventricular thrombi or atrial fibrillation), perhaps 50% to 70% of stroke syndromes that occur are due to the cardiac source and the rest are due to noncardiac disorders.

If a cardiogenic brain embolus is diagnosed, the risk of recurrent stroke within the first month following a cerebral embolic event is about 12% for patients who do not receive anticoagulation.[1] Recurrent emboli to the periphery also occur. Several noncontrolled studies provide evidence that the risk of early recurrence is reduced to 2% to 4% with early full-dose anticoagulation. In addition, in a randomized trial a reduction was noted in recurrent emboli with the immediate anticoagulation of embolic stroke.[74] In that study, patients with suspected embolic stroke underwent CT scanning; 2 patients with hemorrhagic infarcts were excluded, and the remaining 45 patients were randomly assigned to receive either heparin immediately or no heparin. There were no recurrent emboli and no deaths among patients who received heparin immediately but two recurrent emboli and two deaths among patients not receiving heparin.

Overall, the estimated risk of symptomatic brain hemorrhage associated with immediate anticoagulation in patients with aseptic embolic stroke is 2% to 5%.[1] The current recommendations in patients with suspected aseptic embolic stroke are to do a CT scan at 24 hours or later. If there is no evidence of hemorrhage, patients should be anticoagulated with heparin followed by high-intensity warfarin therapy (INR of 3.0 to 4.5); in patients with either large embolic strokes or severe hypertension, anticoagulation should be postponed for several days because of an increased risk of late hemorrhagic transformation. In patients who have hemorrhagic transformation noted on an early CT scan, anticoagulation therapy should not be started until eight to ten days after the event.[1] If there are no recurrences after a year, the warfarin dose should be decreased to a low intensity (INR of 2.0 to 3.0).[1]

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Medical Staff Conference

Current Concepts in Bacterial Meningitis

Discussant
STEPHEN M. HAHN, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

MERLE A. SANDE, MD*: *Bacterial meningitis remains a devastating infection, with a high incidence of attendant morbidity and mortality, especially in patients at the extremes of age. New antibiotics have done little to change this. Much has been learned in the past 10 to 15 years, however, about the pathophysiology of this disease, and new avenues for therapeutic intervention have been opened. Stephen M. Hahn, MD, has reviewed these studies and puts them in clinical perspective in this Medical Staff Conference.*

STEPHEN M. HAHN, MD†: Many advances have been made since the early part of this century in the diagnosis and treatment of bacterial meningitis. The introduction of antibiotics led to a dramatic decrease in morbidity and mortality. Notable advances have not occurred, however, since the introduction of antibiotics; residual morbidity and mortality are still unacceptably high. New methods of therapy beyond the development of antibiotics are required.

Etiology and Epidemiology

Streptococcus pneumoniae, Hemophilus influenzae, and *Neisseria meningitidis* account for more than 80% of the cases of meningitis in adults in the United States.[1,2] *Listeria monocytogenes* and gram-negative organisms cause most of the other 20% of cases. Meningitis is more common in children, with 75% of all cases reported to the Centers of Disease Control in 1978 occurring in patients younger than 5 years.[3] In the neonatal age group (younger than 1 month) group B *Streptococcus* and *Escherichia coli* are the major pathogens. In children older than 1 year and younger than 5 years, *H influenzae* accounts for the majority of cases. Of the three major pathogens in adults, *H influenzae* accounts for about 5% of the cases, *N meningitidis* accounts for 25% to 40%, and *S pneumoniae* accounts for 40% to 50%.[1] Case-fatality rates vary depending on the specific pathogen involved. Most series report the highest case-fatality rate with pneumococcal meningitis. Data from the National Bacterial Meningitis Surveillance Study showed a case-fatality rate of 26% for pneumococcal meningitis, 6% for *H influenzae,* and 10% for *N meningitidis* (Table 1).[2] Overall, in most series, the case-fatality rate for bacterial meningitis is about 10% to 20%.

Diagnosis

The diagnosis of bacterial meningitis is based on recognizing the appropriate clinical features. Two different presentations have been described.[4,5] The first is progressive illness that occurs over a 12- to 24-hour period. Nonspecific signs of fever, malaise, and myalgias occur several days before admission. In the second mode of presentation, the tempo is much quicker and signs and symptoms of meningitis develop over a few hours. Some authors have postulated that a higher bacterial load exists in the patients with the more rapid onset of the disease and claim that a worse prognosis results.

The most important symptoms seen on presentation include fever, chills, sweats, myalgias, confusion, headache, nausea, vomiting, and photophobia. Signs include nuchal rigidity, Brudzinski's and Kernig's signs, fever, and an altered mental state (Table 2). Physicians must not be fooled by a lack of classic signs and symptoms. Some patients with meningitis, especially the elderly and very young, will present with subtle mental state changes and no fever.

Patients with pneumococcal and *H influenzae* meningitis will often have an associated suppurative focus. Otitis media or mastoiditis is seen in 30%, pneumonia in 25%, sinusitis in 10% to 15%, and endocarditis in 5% of patients with pneumococcal meningitis.

The cerebrospinal fluid (CSF) findings are variable. The CSF leukocyte count is usually between 1,000 and 5,000 $\times$ 10^6 per liter (1,000 and 5,000 per μl), although the count may be as low as a few cells or as high as 10,000. Cerebrospinal fluid leukocyte counts nearing 10,000 $\times$ 10^6 per liter should alert a clinician to the possibility of a brain abscess that has ruptured into the subarachnoid space. Polymorphonuclear cells usually account for about 80% of the leukocytes. In patients with *L monocytogenes* meningitis, mononuclear cells may predominate. The CSF glucose level is usually less than 2.2 mmol per liter (40 mg per dl) or less than 50% of the peripheral glucose value. The CSF protein value is usually between 1.0 and 5.0 grams per liter (100 and 500 mg per dl), although levels higher than 10.0 grams per liter (1,000 mg per dl) have been reported.

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ABBREVIATIONS USED IN TEXT

CIE = counterimmunoelectrophoresis
CSF = cerebrospinal fluid

The diagnosis of bacterial meningitis is established by identifying organisms on a Gram's stain or culture of the CSF. In most series, the Gram's stain shows an organism in 70% to 80% of all cases not previously treated with antibiotics. The CSF culture is also positive for organisms in about 80% of all cases.[1,4,5] Administering antibiotics before the lumbar puncture does not change the CSF cell counts or chemistry values but may cause a significant reduction in the diagnostic value of Gram's stains and CSF cultures. Blood cultures are positive for meningitis organisms 40% to 90% of the time.[5,6]

The diagnosis of bacterial meningitis in patients who have previously taken antibiotics has been augmented with the introduction of tests that measure bacterial antigens, the counterimmunoelectrophoresis (CIE) and latex agglutination tests. These tests are no more sensitive or specific than a Gram's stain and culture in patients who have not previously taken antibiotics. The CIE test is available for pneumococci (83 serotypes), *H influenzae* (type b), and meningococci (serogroups A or C). There is no CIE test available for the most common meningococcus that causes meningitis, group B. The sensitivity of the test depends on the specific pathogen involved and varies from 50% to 90%.[1,5] Cross reactions do occur but are relatively uncommon when the test is done properly. The latex agglutination test is more sensitive than the CIE and is less expensive and easier to do.

TABLE 1.—*Bacterial Meningitis Cases and Fatality Rates—The National Bacterial Meningitis Surveillance Study, N=13,974**

Pathogen	Patients No.	Patients %	Fatality Rate, %
Hemophilus influenzae	6,756	48.3	6.0
Neisseria meningitidis	2,742	19.6	10.3
Streptococcus pneumoniae	1,865	13.3	26.3

*Adapted from Schlech et al.[2]

TABLE 2.—*Symptoms and Signs in Bacterial Meningitis**

Finding	Relative Frequency, %
Fever	≥ 90
Headache	80-90
Stiff neck	≥ 80
Brudzinski's sign	50
Kernig's sign	50
Myalgia	30-60
Nausea, vomiting	≥ 80
Altered sensorium	≥ 80
Cranial nerve palsy	10-15
Seizures	20-30
Focal cerebral signs	10-15
Papilledema	< 5
Suppurative foci	0-30

*From Scheld.[1]

TABLE 3.—*A Retrospective Review of 349 Cases of Acute Bacterial Meningitis Over a 25-Year Period*†*

Change	Total Cases	Deaths, %
Mild	111	10
Moderate	118	22
Severe	118	45

*Adapted from Hodges and Perkins.[9]
†$P<.01$.

Sequelae of Bacterial Meningitis

The sequelae of bacterial meningitis are largely neurologic. Global cerebral dysfunction, ranging from simple irritability to confusion, delirium, lethargy, and coma, is most common at presentation. Permanent cerebral dysfunction is a possible sequela. Seizures are most often seen in the pediatric population and occur in about 30% of cases.[1,5] Generalized seizures are not felt to be a poor prognostic sign, especially early in the disease. Focal seizures, however, should suggest the presence of more significant disease. Focal neurologic signs may appear early or late in the course. In early meningitis, focal neurologic abnormalities are a clue to the presence of a brain abscess, Todd's paralysis (after a seizure), or vasculitis with infarction. If focal abnormalities appear late in the course, a more serious disorder is implied, including subdural empyema or effusion, venous thrombophlebitis, abscess, hemorrhage, or infarction. A well-recognized complication of meningitis is cortical vein thrombosis; this occurs ten days to two weeks after the onset of meningitis and results in a strokelike syndrome.[4] Finally, cranial nerve abnormalities accompany meningitis in about 10% to 20% of cases.[1] The eighth cranial nerve complex is often involved, resulting in deafness and ataxia. In one prospective study of children with bacterial meningitis, 10% of the patients had permanent unilateral or bilateral sensorineural hearing impairment. Another 16% had transient conductive hearing abnormalities.[7] Abnormalities of cranial nerves III, IV, and VI also occur, often in patients with increased intracranial pressures. Neurologic sequelae are estimated to be present in about 20% of patients with bacterial meningitis. The highest rates are seen in infants and neonates and with pneumococcal meningitis.

One retrospective study has attempted to assess the subjective outcome of meningitis.[8] Patients were contacted several years after an episode of bacterial meningitis and given a questionnaire asking about residual symptoms. There was no matched control group. Of the respondents, 38% reported residual symptoms including chronic headaches, an inability to concentrate, loss of memory, impaired hearing, visual changes, dizziness, and an impaired ability to function in work or school.

Prognostic Factors

Two important prognostic factors emerge from the literature: the age of the patient and the level of consciousness on admission. Not surprisingly, patients older than 60 years or younger than 1 year have the worst prognosis. Patients who present with substantially reduced consciousness also have the worst prognosis (Table 3).[9] In one prospective study of meningitis, 33% of children who presented with irritability, lethargy, or somnolence were found to have abnormalities on a neurologic examination on discharge.[10(p293)] Of those comatose or semicomatose on admission, 53% had neurologic abnormalities on discharge. In another review of 1,316 cases of meningitis, a significant correlation was found between

TABLE 4.—*Guidelines for Initial and Alternative Antibiotic Regimens in the Treatment of Adult Bacterial Meningitis*

Pathogen	*Initial Choice*	*Alternative*
Streptococcus pneumoniae	Penicillin G	3rd-generation cephalosporin*; cefuroxime; chloramphenicol†
Neisseria meningitidis		
Hemophilus influenzae	Cefuroxime; 3rd-generation cephalosporin*; chloramphenicol†	Trimethoprim-sulfamethoxazole; ampicillin‡
Listeria monocytogenes	Ampicillin	Penicillin G; ? trimethoprim-sulfamethoxazole; ? chloramphenicol†
Gram-negative organisms	3rd-generation cephalosporin*	

*Third-generation cephalosporins should be considered in the following order: ceftriaxone sodium, cefotaxime sodium, and ceftizoxime sodium.
†The use of chloramphenicol should be considered only in patients with both penicillin and cephalosporin allergies.
‡All antibiotic therapy should be tailored to the results of cultures and sensitivities.

TABLE 5.—*A Model for the Pathogenesis of Bacterial Meningitis**

Attaches to the mucosal cells
Transgresses the mucosal barrier
Survives in the bloodstream
Enters the cerebrospinal fluid
Survives in the cerebrospinal fluid
Causes disease in the meninges and brain

*From McGee.[14]

the level of consciousness on admission and the case-fatality rate.[11]

Cerebrospinal fluid values on admission, including the CSF protein concentration, glucose concentration, and leukocyte count, have not correlated consistently with neurologic sequelae or mortality. The duration of illness before admission and the duration of illness before receiving the first dose of antibiotics have been touted as significant but have not been consistently associated with mortality. Prior antibiotic therapy does interfere with the yield of organisms on a CSF Gram's stain or culture but does not significantly affect the neurologic outcome or mortality. Other important microbiologic criteria, including bacterial antigen levels and the density of bacteria on culture, have been correlated with the prognosis in some studies,[6] but confirmation of these findings is still needed. Associated illnesses, including sickle cell anemia, alcoholism, and diabetes mellitus, worsen the prognosis of bacterial meningitis.

Treatment

Despite the conflicting data regarding the prognostic importance of the early administration of antibiotics, it is prudent to begin treatment as soon as possible. Bactericidal antibiotics in concentrations that are well above the mean bactericidal concentration are necessary.[12] The use of an antibiotic before doing a lumbar puncture is controversial. There are some data from studies in animals to support the concept that there is a "golden period" of four hours after the administration of antibiotics during which time the yield of a CSF bacterial culture is acceptable. There are yet no data from humans to support or refute this concept. The decision of when to administer antibiotics should be left to the individual clinician. Nonetheless, antibiotics should always be administered after blood specimens are taken for culture.

Antibiotic therapy is based on the clinician's initial reading of the CSF Gram's stain (Table 4). Intravenous penicillin G or ampicillin is still the most appropriate drug of choice for possible meningococcal, pneumococcal, or listerial meningitis. A third-generation cephalosporin, cefuroxime, or chloramphenicol may be considered as appropriate therapy in penicillin-allergic patients with pneumococcal or meningococcal meningitis or for suspected *H influenzae* meningitis. Therapy should always be tailored to the culture results and sensitivities. The appropriate duration of therapy for meningitis in adults has not been extensively studied, although seven to ten days is considered acceptable.

Pathophysiology

Advances in the understanding of the pathophysiology of bacterial meningitis come largely from studies done in the rabbit pneumococcal meningitis model of Dacey and Sande.[13] These studies have led to an understanding of the inflammatory response to bacterial invasion of the subarachnoid space and of how this is related to neurologic sequelae.

Bacterial meningitis is initiated by one of three mechanisms, a primary bacteremia, direct contiguous spread, or direct entry from trauma. In one model, bacteria attach to a mucosal surface, often the nasopharynx (Table 5).[14] This is followed by movement of the bacteria across the mucosal barrier, their survival in the bloodstream, and seeding of the CSF. Bacterial survival in the bloodstream and CSF depends on their avoiding phagocytosis. The antiphagocytic polysaccharide capsule of the pneumococcus appears to enhance survival.[14] How the bacteria actually cross the blood-brain barrier is unclear. Once they do enter the protected environment of the subarachnoid space, the inflammatory response is initiated and central nervous system tissue damage results.

Changes in the blood-brain barrier occur after the bacteria invade the subarachnoid space. This barrier is thought to be composed of the choroid plexus, the cerebral microvasculature, and the arachnoid membrane.[15,16] It is normally an effective filtering mechanism for the CSF. The capillaries at these sites have tight junctions, unlike the normal fenestrated capillaries elsewhere in the body. In addition, pinocytic vesicles (a common feature of capillaries) are absent and mitochondria are abundant. Infection in the CSF leads to the appearance of pinocytic vesical formation and a separation of tight junctions.[17] This contributes to the entrance of cells and inflammatory exudate into the CSF. Interestingly, only encapsulated organisms cause a separation of the tight junctions.[17]

Host defenses against bacteria within the CSF are limited. In fact, host-defense mechanisms are ineffective in retarding the growth of bacteria in the first 24 hours of experimental pneumococcal meningitis.[18]

There is little or no complement, opsonic, or bactericidal activity present in normal CSF. During acute pneumococcal meningitis in the rabbit model and in humans, only a small rise in complement activity is seen. Only minimal opsonic or bactericidal activity can be measured.[19] Immunoglobulin levels in the CSF do not rise until late in the course of experi-

mental pneumococcal meningitis.[15] The lack of complement activity and specific immunoglobulin are major reasons for the lack of effective host defenses in the CSF. All of these findings suggest that bacterial meningitis represents an infection in the regional area of impaired host resistance.[15]

Twelve hours after infection is initiated in the rabbit model, enhanced chemotactic activity—probably complement-mediated—leads to a CSF leukocytosis.[17] β-Lactam antibiotics may increase the intensity of the inflammatory response by causing lysis of the pneumococcal cell wall. Experimental studies have confirmed that the teichoic acid portion of the pneumococcal cell wall is particularly important in inducing inflammation.[20] The generation of leukocytosis, however, does not appear to be important for host defenses. Ernst and co-workers measured bacterial growth rates and maximal bacterial titers in rabbits rendered leukopenic with the administration of mechlorethamine hydrochloride (nitrogen mustard) and in control rabbits with experimental pneumococcal meningitis (Figure 1).[18] There was no difference in the two groups with respect to bacterial growth rates or maximal bacterial titers. Why the polymorphonuclear cells contribute so little to the control of the infection has not been fully explored. The lack of complement or specific immunoglobulin may be important. In addition, there is evidence that phagocytosis is more efficient in a closed tissue space. The free floating space of the CSF may not allow for sufficient contact for this "surface phagocytosis."[21]

Experimental evidence suggests that the inflammatory response generated in meningitis does not offer protection against invading bacterial organisms. Another line of experimental evidence suggests that it may even be harmful.

The hallmark of bacterial meningitis is the inflammatory exudate within the subarachnoid space. Inflammation causes cerebral edema and increased CSF outflow resistance, which lead to an increased intracranial pressure. Abnormalities in the cerebral blood flow, cerebrovascular autoregulation, and increased CSF lactate levels—a measure of cerebral ischemia—often follow sustained increases in the intracranial pressure.

Cerebral edema is probably the result of both vasogenic and cytotoxic edema. The opening of the capillaries of the blood-brain barrier in response to infection leads to movement of fluid into the interstitium of the brain (vasogenic edema). There is some experimental evidence to suggest that the cytotoxic effects of leukocyte membranes—especially arachidonic acid metabolites—cause edema and direct tissue damage.[22,23] Cerebral edema certainly contributes to increases in the intracranial pressure.

The major compensatory mechanism of the brain to an increased intracranial pressure is the outflow of CSF from the subarachnoid space to the dural venous sinus blood. The CSF outflow resistance is increased in bacterial meningitis, and further increases in the intracranial pressure often occur. Additionally, the removal of potential toxic substances from the CSF is significantly decreased. This is likely from the buildup of inflammatory exudate within the arachnoid villi.[13]

Vasculitis and venulitis commonly accompany bacterial meningitis.[24,25] These vascular changes may have a direct effect on cerebral blood flow and also lead to increases in the intracranial pressure.

The brain exists in a fixed space and has a sophisticated mechanism for controlling its volume to fit this space. Cerebral perfusion pressure is equal to the mean arterial pressure minus the intracranial pressure. As the intracranial pressure increases, the mean arterial pressure must also increase to maintain an adequate cerebral perfusion pressure (a possible explanation for the Cushing's reflex). In experiments conducted by Tureen and associates in the rabbit model, normal autoregulation was determined.[26] Over a wide range of blood pressures, the cerebral blood flow is constant. In infected rabbits, cerebrovascular autoregulation is faulty, leading to a direct effect of the blood pressure on the cerebral blood flow (Figure 2).[26] Tureen and colleagues also showed that as the cerebral blood flow increased, so did the intracranial pressure (Figure 3). To maintain the cerebral perfusion pressure, the mean arterial pressure increases in response to increases in the intracranial pressure. In infected rabbits, this increased arterial pressure leads to direct increases in cerebral blood flow and still further increases in the intracranial pressure. As the intracranial pressure continues to rise, the cerebral

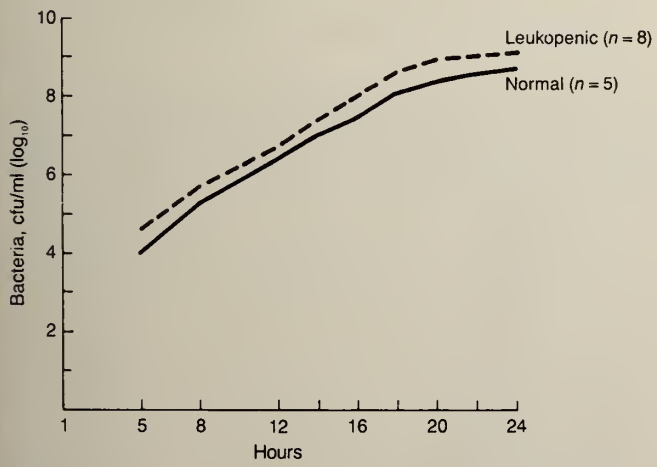

Figure 1.—The graph shows the bacterial growth rates in the cerebrospinal fluid of rabbits with experimental pneumococcal meningitis. Bacterial growth rates in rabbits rendered leukopenic with the administration of mechlorethamine hydrochloride are nearly identical to those of control rabbits with normal leukocyte counts. These data suggest that leukocytes contribute little to the initial host defense against bacterial meningitis (from Ernst et al[18]). cfu = colony-forming units

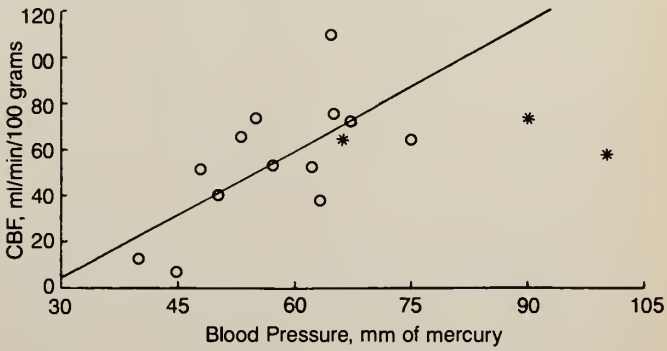

Figure 2.—The graph shows the relationship of the cerebral blood flow (CBF) to blood pressure in experimental pneumococcal meningitis in rabbits. In uninfected rabbits (∗), the CBF is constant over a wide range of blood pressures, showing normal cerebrovascular autoregulation. Increases in the blood pressure in infected rabbits (o) are associated with an increase in the CBF, consistent with a loss of cerebrovascular autoregulation (from Tureen et al[26]). $r = .63$, $P < .02$

blood flow eventually falls, leading to regional or generalized cerebral ischemia. This has possible implications for the control of the intracranial pressure. Volume depletion has been one mode of therapy used to decrease the intracranial pressure. In the rabbit model, decreases in arterial pressure as a result of volume depletion could result in dangerous decreases in cerebral blood flow and worsening cerebral ischemia.

Some of the data from animals regarding cerebral blood flow have been confirmed in humans. Paulson and coworkers measured the mean hemispheric blood flow in patients with pneumococcal meningitis and found it was decreased by 30% to 40%.[27] In addition, autoregulation of the cerebral blood flow was impaired. Goiten and Tamir looked at children with severe bacterial meningitis and found that decreases in the cerebral perfusion pressure below a certain level correlated with morbidity and mortality.[28]

A proposed schema for the pathophysiology of meningitis is given in Figure 4. The inflammatory response leads to cerebral edema and increased CSF outflow resistance, both of which cause an increased intracranial pressure. Such an increase, accompanied by abnormalities in cerebrovascular autoregulation, may lead to a decrease in the cerebral blood flow, ultimately causing cerebral ischemia and parenchymal damage.

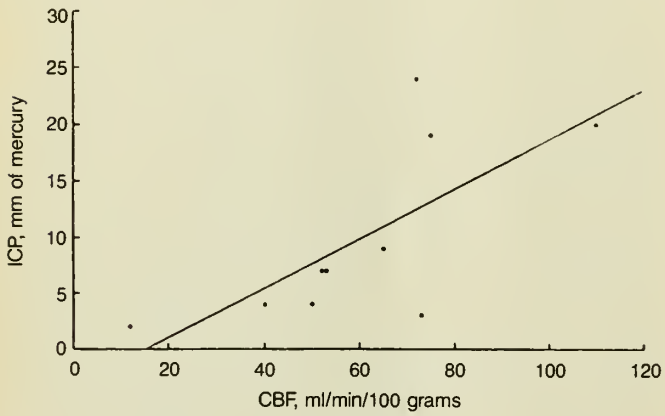

Figure 3.—The relationship of the cerebral blood flow (CBF) to the intracranial pressure (ICP) is shown in infected animals. Increases in the CBF lead to direct increases in the ICP (from Tureen et al[26]). $r = .71$, $P < .06$

Future Therapy

What are the therapeutic implications of the recent developments in the understanding of the pathophysiology of bacterial meningitis? Will interventions that decrease the host inflammatory response lead to decreases in the intracranial pressure and the maintenance of an adequate cerebral blood flow? Will these interventions lead, in turn, to an improved outcome? These questions have only been partially addressed.

Corticosteroids are anti-inflammatory agents used extensively in patients with cerebral edema and increased intracranial pressure. It is postulated that corticosteroids decrease the inflammatory response to bacterial cell wall products, decrease cerebral edema, and decrease outflow resistance in patients with meningitis. This theoretically should lead to the

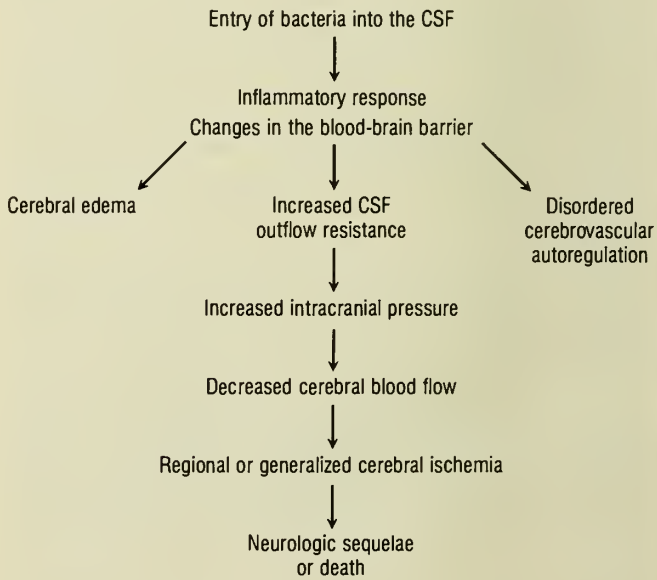

Figure 4.—This schema is proposed for the pathophysiology of bacterial meningitis.

TABLE 6.—*Influence of the Administration of Methylprednisolone Sodium Succinate (2 Doses at 30 mg/kg of Body Weight) and of Dexamethasone (2 Doses at 1 mg/kg of Body Weight) on Manifestations of a 24-Hour Infection With Pneumococci in Rabbits*

	*Mean Results ± Standard Deviation**				
Treatment	*Bacterial Titers, log cfu/ml*	*Leukocytes, $\times 10^9$/liter ($10^3/\mu l$)*	*CSF Lactate, mmol/liter (mg/dl)*	*Change in CSF Pressure, mm of mercury*	*Brain Water, grams H_2O/100 grams dry wt*
No infection†	ND *(11)*	<0.01 *(11)*	1.6± 0.3 (14.0± 2.6) *(11)*	+0.8±1.4 *(11)*	396±14 *(11)*
24-hour infection					
No treatment	7.0±1.2 *(36)*	2.5±6.6 *(27)*	8.4± 2.8 (75.3±25.0) *(18)*	+7.5±6.5 *(19)*	410±11 *(37)*‡
Methylprednisolone	7.6±0.7 *(14)*§	3.9±4.9 *(13)*	7.1± 3.7 (64.3±33.1) *(13)*	+7.8±5.4 *(13)*	395± 9 *(14)*
Dexamethasone	6.7±0.6 *(13)*	2.1±2.2 *(13)*	4.9± 1.4 (43.8±12.3) *(13)*‖	+1.8±2.7 *(13)*#	399±12 *(13)*

cfu=colony-forming units, CSF=cerebrospinal fluid, ND=not determined

*The italicized numbers in parentheses represent the number of animals tested.
†Pooled data are from 7 animals treated with methylprednisolone and 4 animals treated with dexamethasone.
‡$P < .02$ in comparison with other groups.
§$P < .05$ in comparison with dexamethasone-treated group.
‖$P < .01$ in comparison with untreated infected animals.
#$P < .02$ in comparison with other groups infected for 24 hours.

TABLE 7.—*Two Prospective, Double-Blind, Placebo-Controlled Trials of Dexamethasone in Infants and Children With Bacterial Meningitis**

End Point	Placebo	Dexamethasone	P Value
Death	1	0	NS
Moderate to severe hearing loss	13	3	<.01
Requires hearing aid	12	1	<.001

*Adapted from McGee.[14]

maintenance of an adequate cerebral blood flow, a reduction in cerebral ischemia, and less morbidity and mortality. The evidence that corticosteroid use has some of these beneficial effects is just beginning to unfold.

Scheld and associates have shown that penicillin G therapy in rabbits with meningitis did not change the increased resistance to CSF outflow seen, whereas the addition of methylprednisolone decreased both the CSF outflow resistance and the intracranial pressure.[29] Studies by Tauber and colleagues in the same model showed that ampicillin therapy sterilized the CSF and decreased the brain water content, but did not decrease the intracranial pressure.[30] The use of methylprednisolone decreased the brain water content but did not reduce the intracranial pressure. Only the use of dexamethasone substantially decreased the brain water content, the intracranial pressure, and CSF lactate levels (Table 6). Syrogiannopoulos and co-workers showed in an experimental *H influenzae* meningitis model that the use of dexamethasone also decreased brain edema, intracranial pressure, and CSF lactate levels.[31]

Uncontrolled trials and anecdotal reports of corticosteroid therapy in humans with meningitis over the past 20 to 30 years have suggested beneficial effects. Two prospective trials using corticosteroids in patients with meningitis were carried out in the 1960s. DeLemos and Haggerty evaluated the use of methylprednisolone in a randomized placebo-controlled trial of 117 children with bacterial meningitis.[32] No differences between the two treatment groups were seen with respect to neurologic sequelae or mortality. Belsey and associates conducted a randomized placebo-controlled trial of the use of dexamethasone in children with bacterial meningitis.[33] They found a larger incidence of neurologic sequelae in the placebo-treated group. The authors discounted their results, however, because they felt that the placebo group contained more patients with poor prognostic factors. Some of these factors have not been found to correlate significantly with the prognosis.

Lebel and colleagues recently reported two prospective, randomized, placebo-controlled trials of dexamethasone therapy in 200 infants and children with meningitis (Table 7).[34] There was no difference in mortality. Moderate to severe bilateral sensorineural hearing loss and the requirement for hearing aids were substantially reduced in the steroid-treated group. These results are promising. Gastrointestinal bleeding of an unclear cause occurred in two patients treated with dexamethasone. Adverse side effects of dexamethasone use were not otherwise noted. Theoretic concerns remain. A persistence of pneumococci in the CSF well into the course of therapy has been reported in children with meningitis who received corticosteroids.[35] Further trials examining the safety and efficacy of corticosteroid therapy will be necessary in adults.

It is difficult to generalize from the results of the study of Lebel and co-workers to adults. A prospective, randomized, placebo-controlled trial of the use of corticosteroids has not been completed in a group of adult patients with meningitis. Because of this, corticosteroids cannot be recommended as routine therapy in adults with bacterial meningitis.

Other agents that reduce inflammation, like superoxide dismutase or nonsteroidal anti-inflammatory drugs, are being studied to further modify the inflammatory response in bacterial meningitis. As further advances are made in the understanding of the pathophysiology of bacterial meningitis, exciting therapeutic alternatives will be developed. The hope is that these therapies will reduce the residual morbidity and mortality of this disease.

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Epitomes

Important Advances in Clinical Medicine

General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Advances in Liver Transplantation

LIVER TRANSPLANTATION is the only definitive treatment for end-stage liver disease. The procedure is increasingly common in the United States, with more than 1,680 performed in 1988 compared with 18 in 1980. This increase is stimulated by improved operative and long-term survival rates, most centers reporting one-year survival figures of 70% to 80% or better in patients who would otherwise die of diseases such as acute fulminant hepatitis, chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary atresia, and inborn errors of metabolism. Most surviving patients return to their pretransplant activities.

The improved survival rates now reported in large series from many centers relate to several factors. Most important, candidates are referred for liver transplantation earlier in the natural course of their disease, before they reach nutritional bankruptcy, advanced encephalopathy, renal failure, severe coagulopathy, and uncontrolled hemorrhage. Physicians caring for patients with liver disease are learning to avoid a right upper quadrant operation, if possible, in patients who are likely to become liver transplant candidates, especially those with coagulopathies. These factors reduce operative risks. The technical aspects of the recipient operation continue to advance, with several centers reporting decreased operating times, decreased blood usage, and an increased use of autologous blood salvaging devices. Triple-drug immunosuppressive regimens—low-dose corticosteroids, cyclosporine, and azathioprine—are widely accepted now, allowing lower doses of each drug with reduced side effects. The monoclonal antibody OKT3 is used more aggressively to treat steroid-resistant episodes of rejection and in some centers is used for induction immunosuppression immediately postoperatively, especially in patients with renal dysfunction.

The availability of suitable donor organs continues to be a major limiting problem. The state of Oregon adopted a routine inquiry law in 1985, and 43 other states have now passed similar statutes. It is not yet possible to determine if this will help alleviate the problem.

An additional solution to the organ supply problem is the development of techniques for the simultaneous procurement of liver and pancreas grafts despite the common vascular supply. A key development in liver transplantation is the method of the ex vivo preservation of grafts using the University of Wisconsin solution. Many centers are reporting excellent graft function after periods of ischemia of as long as 24 hours compared with 8 hours previously. This solution has not only provided better graft function but also expanded the acceptable donor pool, allowed for further travel to donors, allowed a semi-elective approach to the recipient operation, and lowered costs.

Nowhere is the paucity of size-matched donor organs more devastating than in infants and children. This problem has been addressed recently by reducing the size of the graft with partial hepatectomy and implanting the remaining portion of the graft.

Liver transplantation has forced us to ask questions about our capacity to develop new and expensive therapeutic modalities as health care costs increase. The Oregon legislature took a provocative position in this allocation issue by discontinuing Medicaid payment for extrarenal transplantation, a decision they are reconsidering. These ethical issues are important and force society and physicians to scrutinize the cost-effectiveness of new therapies in promising areas of advancement. It is equally important to subject established medical practices to a similar scrutiny.

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Noninvasive Vascular Diagnosis

ADVANCES IN THE FIELD of noninvasive vascular diagnosis continue at a rate sufficiently rapid to render most summaries of new developments obsolete by the time of publication. A burgeoning technology, coupled with active research efforts in many centers, ensures that the explosive development characterizing this field will continue. The result of this activity is the current availability of a panoply of testing modalities that, taken together, provide a scientific foundation on which to base an objective diagnosis of the presence and

severity of arterial and venous disease in all areas of the body.

Duplex scanning, a technique that combines the use of real-time B-mode ultrasound imaging with a computerized analysis of frequency data from pulsed-Doppler signals from the pertinent arteries, has emerged as the technique of choice for evaluating the extracranial cerebral vessels. Using this technique, competent operators can detect both the presence and severity of disease in the carotid and vertebral arteries with an accuracy exceeding 90%. In addition to its important clinical role, duplex scanning is an accurate research method, and data obtained using this technique have been the primary source of our recent improved understanding of the incidence and natural history of carotid artery disease, as well as the outcome of therapy. Sufficient information is available to accurately determine risk categories based on patient characteristics and duplex scan results. The screening of asymptomatic patients with risk factors for cerebrovascular disease is now eminently justified.

The rapid expansion of therapeutic methods being applied to peripheral arterial disease—conventional surgical procedures, balloon angioplasty, laser angioplasty, atherectomy with rotating or cutting tips (or both), thrombolytic therapy, and new pharmacologic agents—mandates the objective assessment of indications and results. Impressive evidence has been accumulated that the prognosis for patients with peripheral arterial disease is more closely related to the magnitude of objective changes in distal extremity pressures and waveforms than to any combination of symptoms or angiographic findings. Similarly, the results of treatment of any type can only be accurately assessed by comparing before and after procedure pressures, waveforms, and treadmill walking distance, rather than by symptoms or by the angiographic demonstration of patency. A major advance in the postoperative follow-up of lower extremity bypass grafts has been the finding that a decreased graft flow velocity, as determined by the duplex scanner, is a reliable indicator of a failing graft that occurs before the loss of distal pulses, a decrease in ankle pressure, or the occurrence of symptoms. This finding has permitted the salvage of many grafts that previously would have failed. It is clear that the diagnosis, prognosis, selection of therapy, and evaluation of the results of therapy in peripheral arterial disease all rely heavily on noninvasive testing for optimal results. Again, regular periodic screening of asymptomatic patients at risk, as well as of those treated both operatively and nonoperatively, is indicated.

The noninvasive evaluation of visceral arteries is prompted by a desire to detect renovascular hypertension and chronic mesenteric ischemia. The recent improvement in duplex scanning instruments, including phased-array ultrasound and color-Doppler imaging, has resulted in improved diagnostic capabilities in this area. Reliable criteria exist to permit the accurate diagnosis of renal artery stenosis. An inability to successfully image the renal arteries of all patients remains a problem, although much less so than with previous instruments. The superior mesenteric and celiac arteries can be imaged and flow data obtained.

The noninvasive detection of venous thrombosis has most often been done by using indirect plethysmography combined with the use of the hand-held Doppler. The improvements in duplex scanners cited earlier have resulted in this direct method being applied to venous diagnosis as well, with greater accuracy. In particular, the use of color Doppler permits the accurate detection of nonocclusive venous thrombosis and the reliable diagnosis of calf vein thrombosis in many patients. The current accuracy of venous thrombosis testing using duplex scanning exceeds 90% and establishes this as the diagnostic procedure of choice.

Testing for chronic venous disease using the duplex scanner, as well as photoplethysmography, permits a reliable detection of valvular incompetence, chronic venous obstruction, and elevated venous pressures. This testing is ideally suited to evaluate indications for, and results of, any venous reconstructive procedure.

The use of the duplex scanner to evaluate renal transplants has resulted in reliable criteria for the noninvasive diagnosis of acute allograft rejection, as well as of arterial and venous thrombosis or stenosis.

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Preventing Postoperative Thromboembolism

THE INTRODUCTION OF the low-dose-heparin concept more than a decade ago seemed to offer the promise of a simple, safe, and effective means of preventing postoperative thrombophlebitis and, more important, of decreasing the risk of related pulmonary embolism. The administration of 5,000 units of heparin subcutaneously two or three times a day was straightforward, and an international cooperative study of thromboembolism prophylaxis following hip operations seemed to verify its effectiveness.

Nonetheless, there has been considerable disillusionment with the concept. We found no apparent benefit in a randomized group of trauma patients. When bleeding complications occurred, they were always considered to be caused by the drug, even though there was no difference in the incidence of bleeding complications in the two groups.

The rationale for using low-dose heparin is that heparin functions primarily as an antithrombin III cofactor, greatly augmenting its antithrombotic effect. The fallacy of this concept is that if a patient has a condition such as disseminated cancer, severe trauma, shock, or major tissue injury, the clotting tendency generated by these states depletes antithrombin III so that heparin is not functional. This difficulty of predicting whether a given dose of heparin will be effective has diminished enthusiasm for its use.

Factors that seem to decrease the risk of postoperative thromboembolism are early ambulation, elastic compression, leg elevation, the administration of dextran, and the use of intermittent pneumatic compression. Of these, early ambulation has clearly established itself as relieving stases and has become a fundamental aspect of surgical care. Maintaining good hydration, thus ensuring good extremity perfusion, is also a basic aspect of care, but its importance has not been as well recognized.

When a patient is bedridden, elevating the limb is beneficial but uncomfortable and difficult to maintain, particularly in elderly patients. Elastic stockings or elastic compression when tight enough to be effective may not be tolerated by a patient.

In severely ill patients, the greater clotting tendency requires more potent therapy. Low-molecular-weight dextran, a viscosity-lowering solution, provides effective prophylaxis. On the day of an operation, 1 to 2 units are administered, followed by 1 unit given daily for the first three to four postoperative days.

Intermittent pneumatic compression has proved to effectively prevent clot formation. The original rationale was that it squeezed blood out of the leg and prevented stasis. It now seems that calf muscle compression works by activating fibrinolysis; hence, the effect may be not only local but systemic. The disadvantages are its cost and patient discomfort.

Finally, there is a group of patients at high risk who have a history of clotting complications. Many of these patients, when studied with sophisticated tests, will be found to have some abnormality of blood antithrombotic or fibrinolytic factors. This group is best treated by carrying out an operation using heparin or sodium warfarin anticoagulation and the bleeding risks accepted. Heparin can be administered by continuous intravenous infusion in amounts sufficient to raise the partial thromboplastin time slightly. With the use of warfarin, the infusion is started several days before the operation and the prothrombin time maintained at 15 to 20 seconds.

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Restoration of Renal Function by Renal Revascularization

RENAL REVASCULARIZATION is most commonly done to ameliorate renin-mediated renovascular hypertension. Recently, however, a growing body of clinical evidence indicates that such a procedure restores significant excretory function as well, even in kidneys that have minimal to nonexistent preoperative function.

The salutary effects of revascularization on renal function were reported in 1960 in eight patients in whom pronounced renal failure was reversed. More recent publications in 1980 and 1985 have documented clinical, biochemical and radiographic improvements in renal function in 47 kidneys that were nonfunctional before revascularization.

The clinical recognition of poorly functioning kidneys most commonly occurs in the course of an evaluation for renovascular hypertension. Laboratory evidence—blood urea nitrogen and creatinine values—of renal excretory dysfunction is absent. Unilateral renal artery occlusion with nonvisualization of kidney parenchyma is seen arteriographically. A less common clinical presentation but one that is important to recognize is a case of hypertension with underlying atherosclerotic vascular disease and laboratory evidence of renal failure. The onset of renal failure is characteristically rapid, and dialysis may be necessary. An arteriogram shows severe bilateral renal artery disease with minimal to no function. This subset of patients benefits most from revascularization because it restores sufficient renal function to eliminate the need for dialysis.

The recognition that revascularization can restore valuable renal function and ameliorate systemic hypertension has changed the surgical approach to patients with nonfunctioning kidneys. Whereas primary nephrectomy was used liberally in the past, it is rarely indicated today. The operative strategy is directed towards revascularizing all kidneys. Such a strategy is possible when the distal and segmental branches of the renal artery are patent and the renal parenchymal length is 5 cm or more. In the few patients where this is not the case, primary nephrectomy is advisable. Revascularization is usually accomplished by an aortorenal bypass. The gastroduodenal artery on the right and the splenic artery on the left may also be employed to revascularize the kidney. Using these celiac branches has the advantage of eliminating the need to cross clamp the aorta, and the operation can be accomplished nicely through a subcostal incision.

The long-term follow-up of patients undergoing revascularization shows considerable late mortality within two years. Death is not related to renal failure since improved renal function is maintained. Rather, coronary artery disease and myocardial infarction are the causative factors. Attention to cardiac risk factors and symptoms is thus important in maximizing the therapeutic benefit of revascularization.

The benefits of renal revascularization on renal function can be substantial, but certain questions remain to be answered, such as what the role of revascularization is in a patient who does not have hypertension but has severe renal artery disease. Many authors think correction of these "asymptomatic" stenoses improves and preserves renal function, but data are lacking to confirm this contention. Can clinical, biochemical, or radiographic preoperative predictors of the successful retrieval of renal function be defined? Several criteria have been proposed to be predictive, but none are absolute. Answers to these and other questions are needed to optimize the therapeutic effects of renal revascularization on renal excretory function.

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Hernioplasty Procedures for Inguinal Hernia

THE TREATMENT OF HERNIAS continues to be an important topic in the surgical literature primarily because the recurrence rate following hernia repair remains unacceptably high. The excellent results reported by many authors are unfortunately due to short or incomplete follow-ups and not the skill of a surgeon or the particular technique used for the repair. Patients with recurrent hernias frequently attribute the problem to their surgeon and consequently do not return to that surgeon for repair of the recurrence. This factor gives

surgeons a false sense of security in their ability to repair hernias without the complication of recurrence.

The reported incidence of hernia in the United States is 15 per 1,000. The actual incidence is probably substantially higher because a careful physical examination of asymptomatic persons often reveals small inguinal hernias, especially in men and premature infants. In the United States, indirect inguinal hernia accounts for about 50% of hernias. About 25% to 28% of hernias are direct inguinal, 10% to 12% ventral incisional, 6% femoral, 3% umbilical, and 3% are other hernias. Three basic factors, alone or in combination, are responsible for hernias recurring: patient constitution, such as obesity or constipation; operative technique, such as poor suture placement or a missed indirect sac; and operative complications, such as infection or hematoma. The generally reported incidence of inguinal hernia recurrence at five years is 0% to 20%.

Hernias have both economic and medical importance. They decrease productivity by causing pain, limiting motion, and sometimes causing simple or strangulated intestinal obstruction. The development of a hernia may also be associated with other medical conditions. A continued decrease in the morbidity and mortality of hernia repair is due to improvements in surgical and anesthetic techniques and to the recognition and correction or optimization of coexisting medical conditions, particularly in the elderly. Recognizing and treating factors that produce increased intraabdominal pressure or contribute to infection, before hernia repair, increase the likelihood of a successful repair.

The specific repair used for inguinal hernias varies considerably among surgeons, and each repair has its advocates who have good results with a given technique. In the United States the most commonly used repair for indirect inguinal hernia is the Bassini repair and for direct inguinal hernia are the Bassini, Cooper ligament (McVay), and the Shouldice repairs. While there is considerable variation in the reports of recurrences following the Bassini and Cooper ligament repairs, most surgeons reporting the results of the Shouldice repair have consistently reported five-year recurrence rates—0.7% to 1.3%—equal to and often superior to the best results reported for other repairs. The use of a synthetic mesh in primary inguinal hernia repairs has been recommended for the larger and more complex hernias and has a reported recurrence rate of 0% to 4% in several small series.

Outpatient inguinal hernia repair has been shown to be safe, acceptable to patients, and highly cost-effective for most patients. Patients with significant cardiac and respiratory disease, labile hypertension, and insulin-dependent diabetes mellitus or with large hernias are generally best managed as inpatients. The use of 0.5% bupivacaine hydrochloride as a long-acting local anesthetic even when general anesthesia is used appears to be a major factor in patients' acceptance of outpatient hernia surgery. Early ambulation, the avoidance of bladder distension, and adequate pain control are considered the keys to the success of outpatient hernia repair. Recurrence rates of inguinal hernias done using local anesthesia are equal to those done using general anesthesia.

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Symptomatic Carotid Artery Disease

EXTRACRANIAL CAROTID ARTERY DISEASE is associated with stroke or transient ischemic attacks by three possible mechanisms: emboli, hypoperfusion by flow reduction, and intracerebral propagation of thrombus following occlusion of the internal carotid artery. About 80% of all strokes are thromboembolic in origin. While rare conditions such as fibromuscular disease, aneurysms, and arteritis contribute to this figure, the overwhelming majority of these events are complications of atherosclerosis. A strong correlation between neurologic events and angiographically evident atherosclerotic carotid bifurcation disease has been thoroughly demonstrated. A complex plaque in this region serves as a prime source of cholesterol-fibrin or platelet-aggregate emboli from plaque ulceration. Intraplaque hemorrhage often precedes plaque ulceration. A bifurcation plaque may also cause stenosis of the proximal internal carotid artery; flow limitations will occur if the stenosis is severe (>80% of the area). Symptoms may occur if collateral flow is inadequate. Should total occlusion of the internal carotid occur, propagation of thrombus into the intracranial portion may cause symptoms days later when clot reaches the retinal or middle cerebral vessels.

Hemispheric and retinal symptoms and deficits are classic for carotid disease. Depending on the anatomic situation, however, carotid disease may also contribute to basivertebral or global hypoperfusion symptoms. The pattern of symptoms may be important, as recurrent identical hemispheric symptoms are typical of a carotid embolic source. Chronic ocular ischemia may cause various subtle visual symptoms and signs that should arouse a suspicion of carotid occlusive disease, particularly when not associated with overt retinal disease or hematologic abnormalities. The absence of a cervical bruit in a symptomatic patient should not deter one from looking for carotid occlusive disease.

The possibility of a carotid source of an ischemic event or state should prompt a minimum evaluation with a carotid echo-Doppler scan. In experienced hands, these scans are more than 90% accurate in identifying carotid stenosis and ulceration. They also provide an estimate of plaque "softness," an indicator of increased propensity for embolization. Nonhemispheric symptoms may be further evaluated by physiologic studies such as oculopneumoplethysmography. Isotopic cerebral flow studies also show promise for further clarifying low flow states. Angiography remains the mainstay of the diagnosis of carotid disease and should include intracranial views. Computed tomography (CT) and magnetic resonance imaging can be useful in defining chronic degenerative changes, the presence and location of an infarct, and the age of an infarct by the degree of CT contrast enhancement. This latter study indicates infarct maturation and when operative relief of a tight internal carotid stenosis will be less likely to cause reperfusion injury to the periinfarct zone.

The treatment of symptomatic carotid disease continues to be controversial. Commonly lost sight of is that the goal of

treating carotid disease, medically or surgically, is to prevent stroke—the rare exceptions being where global ischemia causes disabling symptoms. Studies that focus on late survival as an end point and that do not randomly assign symptomatic patients according to the degree of carotid stenosis or ulceration are numerous. Such studies beg the question of whether there is a subset of patients who have experienced transient ischemic attacks or a limited completed stroke and who have a territorially appropriate carotid lesion and can have their chance of future stroke diminished by a particular form of therapy.

The medical treatment of cerebrovascular disease involves the control of hypertension and antiplatelet therapy. Hypertension remains a critical factor in cerebrovascular morbidity. It has been suggested that improved hypertension treatment is responsible for the decrease in the national stroke rate since 1970, but this remains unproved. Antiplatelet therapy has become a mainstay of the treatment of transient ischemic attacks despite most studies showing no stroke-preventive benefit over placebo, only decreased late mortality; 15% to 20% of patients in the "aspirin trials" have gone on to completed stroke within two years.

Scattered reports have appeared of intraluminal balloon angioplasty of carotid bifurcation atherosclerotic stenoses and internal carotid fibromuscular disease. Close monitoring and careful evaluation will be necessary before welcoming or condemning this technique.

Operative intervention for symptomatic carotid disease has been shown by numerous studies to substantially benefit patients with significant stenotic or ulcerative lesions and ipsilateral ischemic events. The stroke rate following a carotid operation would appear to be 1.0% to 1.8% per year for patients with hemispheric symptoms and lower for patients presenting with amaurosis fugax. The comparative stroke rate for patients with transient ischemia treated medically is at least 5% a year. It should be recalled that this figure includes patients with no or minimal demonstrable carotid disease and almost certainly underestimates the natural history of transient ischemic attacks in that cohort with significant carotid disease. Published perioperative stroke and mortality statistics indicate that a carotid operation can be done safely—combined stroke and death rate less than 4%—by experienced surgeons with the proper patient selection. Some series have shown unacceptable results. It is incumbent on each surgeon who does carotid surgery to approach this procedure only with the appropriate indications, to operate with the utmost respect for the potential morbidity, and to constantly review his or her own statistics.

Carotid bifurcation endarterectomy in well-selected cases will result in the relief of hemispheric symptoms with near certainty, a lower recurrent stroke rate for those patients with limited fixed deficits, and the relief of basivertebral and global symptoms in 50% to 70% of cases. The best results in this last category are obtained in patients with classic posterior circulation symptoms, a highly stenotic internal carotid artery, and angiographic posterior circulation compromise. External carotid reconstruction may help selected patients with internal carotid occlusion and definite hemispheric symptoms, particularly if the middle cerebral artery is supplied from that stenotic artery angiographically. Patients with hemispheric transient ischemic attacks and relatively normal carotid arteriograms appear to be at a lower risk for late stroke, particularly if they have had only a single event. Those with multiple events require more careful follow-up with noninvasive examinations.

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Bleeding, Clotting, and the Use of Blood Products in Trauma Care

IMMEDIATELY AFTER SERIOUS INJURY, the ability to limit bleeding from injured tissues largely determines the outcome. For trauma surgeons, there are few situations more harrowing than dealing with a seriously injured patient who has had a breakdown in hemostatic mechanisms. Various approaches designed to prevent such a loss of hemostatic control have been proposed, and some have gained considerable popularity. Whether they are scientifically correct and clinically beneficial is sometimes doubtful.

Several factors are known or suspected to contribute to a breakdown in hemostasis in an injured patient. Preexisting major abnormalities are fortunately rare and usually related to the use of therapeutic drugs. Anticoagulation with vitamin K antagonists is one of the few legitimate indications for the prophylactic use of fresh frozen plasma. Significant hepatocellular insufficiency is another. Hypothermia is one of the avoidable causes of impaired hemostasis and is probably one of the most underestimated in its importance. Hypothermia impairs various steps in the coagulation sequence and seems to have a remarkably strong effect on platelet function in vivo. Hypoperfusion is emerging as perhaps the key causal element in those few patients who have a true systemic breakdown in hemostasis. This concept has been strongly confirmed by almost all the experimental work in this area and has recently been supported by clinical data. The sooner bleeding is stopped and the blood volume restored, the less probability there is of a coagulopathy developing. This effect of sustained and severe hypoperfusion accounts, at least in part, for the association of impaired hemostasis with a massive transfusion.

Massive transfusion deserves special comment because it has become the focus of prophylactic interventions. Stored blood is variably deficient in some coagulation factors (primarily V and VIII) and is totally devoid of functioning platelets. Therefore, a dilutional or washout effect is anticipated and much feared. Various detailed studies of heavily transfused patients have not shown clinically significant coagulation component deficits, however, except in those with clinically obvious impaired hemostasis in whom the deficits are much greater than can be accounted for by dilution. Factors V and VIII are particularly well maintained because of their rapid rates of synthesis, but these are the two that are depleted in stored blood. Platelets are of a more rational concern, and the platelet count is certainly driven down by dilution in heavily transfused patients. Almost all studies in transfused patients and the pertinent studies in patients un-

dergoing therapeutic plasmapheresis show great difficulty in driving the platelet count below 50×10^9 per liter (50,000 per μl) in patients with intact marrow function. Most important, the hypothesis that giving platelets prophylactically will make a difference in seriously injured, heavily transfused patients has been tested in a randomized prospective trial in Seattle. There was little effect of the prophylactic administration of platelets on the platelet count and no effect on any criterion for bleeding.

The main reason to be selective is that the use of fresh frozen plasma and platelets can transmit serious or lethal infections. The acquired immunodeficiency syndrome has the public's attention at the moment. More important is transfusion-transmitted non-A, non-B hepatitis. It is highly doubtful that the prophylactic administration of fresh frozen plasma and platelets in most transfused injured patients does more good than harm, an opinion recently affirmed by the consensus conferences of the National Institutes of Health.

A recognition of the risk of disease transmission with transfusion has altered the practice of most trauma surgeons. There is now greater emphasis on blood salvaging techniques and autotransfusion. There is general acceptance that lower hematocrits are safe in the average young trauma patient, and the old rule of giving "2 units" of blood automatically when a transfusion is required has been—or should be—abandoned. Many surgeons now question the wisdom of the nonoperative management of solid organ injuries, as patients with these injuries average twice the number of transfusions as those treated surgically.

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Surgical Treatment of Peptic Ulcer Disease

ALTHOUGH THE FREQUENCY of hospital admissions for peptic ulcer disease was decreasing even before the introduction of H_2-receptor antagonists in the United States in 1977, since 1977 the number of operations for peptic ulcer disease has decreased considerably. In addition to H_2-receptor antagonists, sucralfate (a surface-active agent) has been increasingly used in recent years for the medical management of peptic ulcer disease. In the near future, proton pump blockers will provide nearly complete control of acid secretion. In the face of improved medical management, the nature of the surgical treatment of peptic ulcer disease has changed. Overall, fewer operations are being done than in previous years. A greater percentage of patients are being operated on for the complications of peptic ulcer disease—hemorrhage, perforation, and pyloric obstruction—than for intractable peptic ulcer disease. Those patients who are treated surgically tend to be older and sicker than in previous years, with resultant increased morbidity and mortality.

In addition to the classic operations for peptic ulcer disease—antrectomy with truncal vagotomy and truncal vagotomy with a drainage procedure—the proximal gastric vagotomy (PGV) has been increasingly used for peptic ulcer disease over the past few decades. Although its recurrence rate approaches 15%, the PGV offers less postoperative morbidity (diarrhea and dumping) than the classic operations. For this reason, many consider it the operation of choice for intractable, uncomplicated duodenal ulcer disease. The PGV is also being increasingly used in patients with perforated duodenal ulcers who are considered candidates for a definitive ulcer operation at the time of plication. It has been recommended by some investigators for use in bleeding or obstructing duodenal ulcers and in gastric ulcers but still must be viewed as unproved in these cases. For bleeding duodenal ulcers, oversewing of the bleeding vessel with the truncal vagotomy and pyloroplasty or truncal vagotomy and antrectomy remains the standard. For obstructing duodenal ulcer, a truncal vagotomy and gastrojejunostomy or truncal vagotomy and antrectomy remain the standard operations. For type I gastric ulcers—those to the left of the gastric angulus without associated pyloric or duodenal disease—antrectomy without vagotomy remains the standard operation. For prepyloric ulcers, the PGV has a high recurrence rate, and most surgeons would favor the use of a truncal vagotomy and antrectomy.

Although surgical practice in peptic ulcer disease has changed in recent years, general surgeons must be familiar with all of the operations for peptic ulcer disease and tailor the operation to the given situation of each patient.

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Vascular Endoscopy

ENDOSCOPY OF THE VASCULAR SYSTEM has evolved over recent years from an experimental research procedure to a sophisticated diagnostic and therapeutic adjunct for surgical or percutaneous interventions of the peripheral vascular and coronary circulation. Advances in fiber optics and medical electronic imaging systems now allow the production of flexible angioscopy catheters, which incorporate a fluid irrigation channel, in diameters of 2 mm. Ultrafine instruments down to 0.2 mm are also being investigated.

Intraoperative angioscopy is done by introducing the endoscopic catheter through the vessel incision made for a bypass or other procedures. An objective lens transmits the image through a coherent bundle of several thousand quartz fibers to a video camera and magnification system, with a color image projected onto a TV monitor. Flushing of a heparinized saline solution through the irrigation channel clears blood from the field of view and provides a superb three-dimensional view of the vessel interior.

Applications include the verification or further elucidation of ambiguous angiogram abnormalities—including more accurately estimating the severity of stenosis and plaque morphology and differentiating thrombotic occlusion from atherosclerotic processes—the inspection of anastomotic suture lines to exclude technical faults, the identifica-

tion of venous valves and major tributaries during in situ saphenous vein bypass, monitoring remote intraluminal procedures such as balloon catheter thromboembolectomy or dilatation, and the assessment of the immediate results of newer treatment modalities, especially laser angioplasty and atherectomy. A selective use provides an adjunct to intraoperative arteriography in some cases and allows the omission of radiologic monitoring in others. For example, during balloon-catheter thromboembolectomy, angioscopy provides direct inspection of the vessels—arterial, venous, prosthetic graft, or dialysis shunt—containing thrombus or embolic debris, a visual monitor of the thrombectomy procedure, and an immediate examination of the lumen after instrumentation. Angioscopy also has an increasing role in cardiovascular research, providing unique information on the pathogenesis of vascular diseases and the mechanisms of various forms of angioplasty devices in a controlled environment.

Coronary angioscopic examinations have provided new insights into the nature of coronary ischemic syndromes, particularly with reference to the respective roles of spasm, stenosis, plaque ulceration, and thrombosis. Stable angina pectoris has been seen to be mainly associated with smooth, nonulcerated atheromatous lesions whereas unstable or accelerated angina is more frequently associated with endothelial ulceration, thrombus, and microembolization. Intraoperative inspection of coronary bypass anastomoses has revealed intimal flaps and suture irregularities in a small percentage of cases; these findings may lead to a revision.

Percutaneous vascular endoscopy is also becoming practical, using specially designed vascular cannulae and delivery catheters. These techniques remain investigational and are largely restricted to "downstream" examinations because of the problem of imaging in a flowing bloodstream. Percutaneous systems for coronary endoscopy are being developed.

The limitations of current angioscopy techniques and equipment include a lack of precise steerability, instrument fragility, the potential for complications—intimal trauma, fluid overload, and contamination—and the necessity for experience in the specialized techniques and interpretation of the images obtained. Nevertheless, angioscopy can now be considered an alternative to intraoperative angiography, and it seems inevitable that vascular endoscopy will assume an increasing role in the management of cardiovascular disease.

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Editorials

Medical Education for Today's Practice

MEDICAL EDUCATION for today's practice is of the greatest importance to the medical profession, but it is also of importance to other health professions that share at least part of the theory and the practice. Yet there is much dissatisfaction with medical education within the medical profession and elsewhere, and the dissatisfaction is growing. Admittedly, the task of selecting a person who both wants to be a physician and who will prove to be a good one ten years down the road has so far defied objective description. Most of those accepted into medical schools are well qualified according to the existing criteria, and most do turn out to be conscientious, competent physicians when their training is complete. This completeness is temporary at best, however, if it is not augmented by a lifetime of continued learning and hands-on practice experience. The rapid pace of today's medical progress brooks of nothing less.

But as this modern medical progress was establishing its rapid pace, largely during the present century, some structural anomalies in medical education stemming from the reforms of the early 1900s have become more and more firmly entrenched, and their separate and somewhat special interests tend to be increasingly divisive of the whole. There is danger of losing sight of what medical education is all about—that is, training persons to be physicians competent to take care of patients in the technologic, social, economic, and political health care environment of the day. To be sure, there are other specialized roles that are appropriate for well-trained physicians. Some must do research, some must teach—although this is seldom a full-time occupation—and some must fill important administrative positions in the public and private sectors of the health care system. Some manage to successfully combine one or more of these roles. But the main purpose of all medical education should still be to train men and women to be competent physicians through a lifetime of practice in caring for patients and in health care of the public as this may be more broadly defined.

Now, what might be some of these anomalies that may be divisive in medical education? There may be at least two sets of them. One is the now time-honored separation of the undergraduate, graduate, and continuing segments of what is more realistically an educational continuum over a lifetime of training and practice. Each segment is conducted more or less independently of the others, and each has different goals and to a great extent different sponsorship. In many ways they are quite independent of one another, and often the emphasis is on a scientific discipline rather than on the knowledge, skills, and experience needed to competently care for patients in today's practice world. Another set of what might be called anomalies occurs within medical schools, where the preclinical years are largely separated from the clinical years, and both are considerably shielded from first-hand experience in patient care as it happens in daily practice. Most of the teaching in many medical schools is done by academic faculty who are often engrossed in their own admittedly important specialty and research interests. The preclinical years are usually the responsibility of the basic scientists, and for the clinical years the clinical science departments have the responsibility. And much of what is taught and learned was not known ten years ago, and much of it will need to be replaced perhaps ten years hence.

It seems that in many ways and in many medical schools it is the student who gets short shrift in all of this. Many faculty have conflicts of interest when it comes to teaching students, and what students are being taught at the convenience of the faculty may be what they will never need to know except to pass examinations given by the faculty or by boards made up largely of faculty from various medical schools. These phenomena tend to persist through graduate training, although practice experience within a specialty receives more attention. Nevertheless, students may not be as well prepared for practice when they finish their training as they thought they would be, and this may be because their teachers at both undergraduate and graduate levels were really not well qualified to teach them what they needed to know to prepare for medical practice in the changing scientific, technologic, social, economic, and political world of health care in which they find themselves today. There are disturbing signs that many young physicians now in their early years of practice are in fact not well prepared and are not always coping well with stresses in the quite different, even unexpected, practice environment in which they are trying to conduct themselves. At the very least, one might say that here might be room for some improvement in the continuum of medical education for patient care, with more of a contribution from the practice environment at all levels of medical education.

MSMW

The Nature and Evolving Treatment of Myelodysplastic Syndromes

THE MYELODYSPLASTIC SYNDROMES (MDS) provide a clinical setting for evaluating the evolution of a relatively benign chronic hematologic disorder into a frankly malignant disease similar to acute myeloid leukemia (AML). Primary myelodysplasia, which occurs predominantly in the elderly, and secondary myelodysplasia, occurring with increasing frequency following cytotoxic chemotherapy for other tumors, are disorders that are becoming more common as the population ages and tumor therapy becomes more effective. Major advances in understanding the biologic abnormalities in MDS have recently led to new therapeutic approaches that attempt to alter the possible pathogenetic mechanisms underlying these disorders.

In view of these developments, the review of MDS by Doll and List elsewhere in this issue provides a timely and careful compilation of data regarding the diagnostic and prognostic categorization, hematologic abnormalities, cytogenetic findings, and a discussion of some of the possible pathogenetic mechanisms fundamental to MDS. Patients with these syndromes are characterized clinically by having refractory cytopenias with associated cellular dysfunction and characteristically abnormal morphologic features of the marrow, which demonstrates specific defective myeloid maturation with dysplasia of at least two and generally three hemopoietic cell lines, suggesting a pathologic involvement of the pluripotential hemopoietic stem cell. In approximately 10% to 40% of these patients, the disorder evolves into AML, whereas the majority of these patients have morbidity

ABBREVIATIONS USED IN TEXT

AML = acute myeloid leukemia
CSF = colony-stimulating factor
FAB = French-American-British [Cooperative Group]
GM-CSF = granulocyte-monocyte CSF
MDS = myelodysplastic syndromes
RAEB = refractory anemia with an excess of blasts
RAEB-T = RAEB in transformation

and mortality related to their dominant cytopenias. In addition, because of their elderly age at presentation, concomitant nonhematologic diseases substantially complicate their care. The clinical spectrum of MDS encompasses conditions that have been characterized morphologically in the earlier literature as hemopoietic dysplasia (preleukemia), refractory anemia with an excess of blasts (RAEB), and subacute myeloid leukemia (or oligoblastic leukemia). A subsequent classification by the French-American-British (FAB) Cooperative Group separated these disorders into more precisely defined morphologic categories that overlap somewhat with the previous nosologic classification. As reviewed by the authors, these disorders include refractory anemia with or without ringed sideroblasts, which have a lower degree of myeloid maturation abnormalities than in patients with RAEB or with refractory anemia with an excess of blasts in transformation (RAEB-T). Patients with refractory anemia generally have better prognoses than those with RAEB or RAEB-T: median survivals are 3 to 6 years versus 6 to 12 months, and the incidence of transformation to AML is 5% to 15% versus 40% to 70%, respectively. Analyses of biologic variables such as in vitro marrow cell growth and marrow cytogenetics have indicated the presence of an abnormal clone of hemopoietic cells in these patients. A negative prognostic import has also been shown if these adjunctive studies reveal the presence of abnormal marrow cytogenetics or defective in vitro myeloid clonogenicity (see below).[1,2]

As pointed out in the review, until recently management of these patients' cytopenias has been suboptimal, consisting essentially of symptomatic support with red blood cell or platelet transfusions and antibiotics as needed. Occasional beneficial responses in blood counts have been reported with an assortment of nonspecific agents such as pyridoxine, danazol, and corticosteroids. Such responses, however, are generally limited in incidence, extent, and duration. Bone marrow transplantation, valuable for the rare cases of MDS in young patients,[3] is generally not available for this elderly group of patients. Although sometimes useful for subsets of younger MDS patients, standard cytotoxic chemotherapy has been relatively poor at inducing durable remissions for elderly persons with this syndrome as compared with its efficacy for de novo AML.

Biologic markers such as in vitro marrow cell clonogenic assays and cytogenetics have also been useful in assessing certain critical pathogenetic features in these disorders. Uncoupling between proliferative and differentiative programs in hemopoietic stem cells of patients with MDS and in patients with leukemia has been proposed as a basic biologic lesion within their clonal hemopoietic cells.[4] Because of this cellular defect, maturation-inducing agents such as retinoic acid, vitamin D, and low doses of cytarabine (cytosine arabinoside) have been used in preclinical and clinical trials to treat MDS and myeloid leukemia. Studies in animal models with such agents have indicated that leukemic cell growth is diminished concomitant with enhanced differentiation.[5-8] Although effective in a small proportion of patients, these maturation-inducing agents have had limited impact on effectively managing MDS.[9,10] Whereas treatment with low-dose cytarabine has shown efficacy in a variable proportion of MDS patients, the incidence of such beneficial response is low, worsening cytopenias often occur during therapy, and most responses have been of relatively short duration.[11] The initial results of a recent randomized trial in MDS comparing low-dose cytarabine with supportive care only showed no improvement in survival and a higher proportion of infectious complications associated with therapy.[12]

The development of in vitro marrow clonogenic culture assays led to the discovery of a family of interacting hematopoietic growth factors—the colony-stimulating factors (CSFs)—which have recently been shown to have major physiologic roles for controlling hemopoiesis in vivo.[13] Four CSFs and their specific cell surface receptors—multi-CSF (also called interleukin 3), granulocyte-monocyte CSF (GM-CSF), granulocyte CSF, and monocyte CSF—have been biochemically defined and functionally characterized. Multi-CSF and GM-CSF have predominant proliferative effects on early hemopoietic cell compartments whereas granulocyte CSF and monocyte CSF have major differentiative as well as proliferative effects on later, more lineage-restricted cell populations (granulocytes and monocytes, respectively). Each hemopoietic cell lineage appears regulated by both proliferative and differentiative stimuli. Marrow culture studies in patients with MDS have shown subnormal clonal growth and defective cellular maturation of myeloid and erythroid precursors, which become more abnormal as the disease evolves towards acute myeloid leukemia.[2] Defective proliferation of hemopoietic precursors within MDS marrow has been suggested as being due to either a decreased responsiveness to or production of such hemopoietic factors.

Recently, MDS marrow cells have been found to possess the potential for a myeloid differentiative response to recombinant granulocyte CSF in vitro associated with decreased clonal self-generation.[14] Cytogenetic abnormalities of marrow cells from MDS patients are nonrandom and show frequent involvement of chromosome regions coding for the CSFs and their receptors, particularly in therapy-related—that is, secondary—myelodysplasia.[15,16] A predominant cytogenetic finding in these syndromes is deletion of part or loss of chromosomes 5 or 7, with the abnormalities of chromosome 5 generally being situated in a specific banding region on its long (q) arm.[15,17] Within this region of chromosome 5 are genes coding for GM-CSF, monocyte CSF and interleukin 3, and the monocyte CSF (the c-*fms* oncogene) and platelet-derived growth factor receptors.[16,17] Thus, the altered expression of genes in this and other nonrandomly abnormal chromosomal regions may play a pathogenetic role in these disorders. These data using in vitro culture and cytogenetics have provided a biologic framework defining possible mechanisms for abnormal growth factor responsiveness or production that contribute to the aberrant marrow cell proliferation and differentiation occurring in these syndromes. Such information has led to the recent development of therapeutic protocols using colony-stimulating factors to treat these patients.

The introduction of recombinant DNA technology has generated large quantities of purified human CSFs. These

recombinant hormones have been used in clinical trials, and both granulocyte CSF and GM-CSF have been shown to abort neutrophil nadirs following chemotherapy or chemoradiotherapy and to increase neutrophil counts in patients with certain acquired and congenital neutropenias.[18-20] Recent studies have also used either GM-CSF or granulocyte CSF to treat MDS patients and have shown that these hormones greatly improve blood neutrophil levels and cellular function as well as marrow morphology—that is, enhance myeloid cell maturation patterns—in a high proportion of these patients.[21-23] Both hormones appear to be well tolerated with little associated toxicity, and both can be administered subcutaneously, indicating their potential for treating outpatients. The in vivo and in vitro differentiative responses of marrow precursors from these patients suggest that a decreased intramedullary availability of effective levels of CSFs underlies certain cytopenias in patients with MDS. In a low fraction of such patients, improved hemoglobin levels and decreased erythrocyte transfusion requirements have occurred, whereas platelet counts have generally remained unchanged. Studies are needed to determine whether a combination of CSFs with other growth factors, such as erythropoietin (effective for treating the anemia of chronic renal disease[24]), may provide greater potential for resolving the hypoproductive anemia so prominent in these patients.

A major concern, however, about the use of these growth factors in myeloid clonal hemopathies such as MDS relates to the possible enhanced proliferation of the abnormal marrow cell clones in response to these hormones, which could provoke progression to AML. In this regard, the recent study of Ganser and co-workers using GM-CSF in patients with MDS showed that a substantial proportion (5 of 11 treated patients) underwent blastic transformation during or shortly after such treatment.[22] The poor responses in this study may relate to a high proportion of these patients having RAEB or RAEB-T—that is, with more than 15% marrow blasts. As this group of patients is most in need of effective therapy, this problem may limit the use of GM-CSF for MDS. This complication of blastic progression has not been as yet noted with granulocyte-CSF treatment and may relate to this agent's having a greater differentiative than proliferative function compared with GM-CSF. Some patients in whom AML developed after GM-CSF therapy initially had chronic myelomonocytic leukemia, which is more likely a myeloproliferative rather than a myelodysplastic disorder. These findings indicate the need for a careful morphologic evaluation and clinical characterization before starting therapeutic trials with these agents.

With the availability of recombinant human CSFs, the management of hemopoietic disorders is entering a new era. Despite the demonstration of encouraging improvements in blood counts and marrow morphology in a substantial proportion of MDS patients with these hemopoietic growth factors, however, randomized controlled studies are needed to determine whether the natural history of these disorders (survival, evolution to AML, infectious complications) will be altered by administering granulocyte CSF or GM-CSF. A further dissection of cellular, genetic, and molecular regulatory elements involved in hemopoietic growth factor production and responsiveness should provide major advances in the understanding of these diseases.

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A View From Canada

MOST CANADIANS WOULD AGREE with the conclusion of the article by Kevin Grumbach, MD, elsewhere in this issue, that we in Canada have organized our medical health insurance better than have many other countries. We would certainly agree with his statement, "Health insurance is indispensable in the expensive context of health care today, both to protect against the financial calamity of catastrophic illness or injury and to promote access to basic medical care."

However, while we believe that our system has many advantages over the nonsystem of our great neighbors to the south, some of which have been carefully detailed by Grumbach, we must also admit that the Canadian system is not

without its serious drawbacks. Therefore, those of us who have had a quarter of a century of experience in organizing and working in this system would caution against the over-enthusiastic acceptance of the whole Canadian package without careful scrutiny.

Although health insurance, to use the magnificent phrase of Sir Winston Churchill, "calls the magic of the millions to the rescue of the individual," it is the weakness of democracy that the electorate can award themselves benefits at the expense of others. This tendency is exploited by politicians. Some such benefits, such as universal health insurance, might be a laudable social goal, but danger arises when this goal is accompanied by a weakening or a loss of personal responsibility by persons and their loved ones.

The danger is that the benefit easily evolves into a political right, and rights without responsibility can lead to misuse and heavy costs. The Canadian health insurance plan is an excellent example of how this can happen despite the best possible motivations of many fine Canadians.

In the development of Canadian health insurance, there was always a struggle between those who thought that any system must maintain some personal financial responsibility and those who thought that the whole service should idealistically be "free." In a democracy it is no surprise that the advocates of a free service triumph over those who advocate personal responsibility. By insisting on a free health service, the Canadian Federal Government has put itself into a difficult position. In removing all individual fiscal responsibility, they have taken upon themselves the sole responsibility for the control of costs.

Usually in any transaction between free persons there exists a multitude of personal decisions—whether or not to buy, what price to pay, and in what circumstances. There is always an invisible "police officer of restraint" in every transaction, even in a world of credit cards. Once the transaction becomes a social right and is considered free, then the police officer of restraint has gone and the system is wide open to overuse or abuse by either party—the buyer or the seller.

In the emotionally charged field of modern preventive, diagnostic, or therapeutic medicine, it is difficult to define exactly what service is necessary and what is unnecessary, so systems of central control just do not work. Costs, therefore, which are going to go up inevitably for many good reasons, also go up for bad reasons. Not only do some patients overuse medical services, but most of us would agree with Grumbach's statement, "fee-for-service reimbursement has its own financial incentives to overtreat patients." We also agree with his assessment of the disadvantages of other methods of payment.

While Canadian patients, relieved of any personal responsibility, remain content as they enjoy an excellent service, the fact is that they have not been asked to pay for this, either by adequate premiums, by increased taxes, or at the level of service. Our politicians, rather than insisting on pay as you use, have just picked up the tab. This has contributed to an increasing Canadian national deficit, which is now so large that recently it attracted the unfavorable attention of the International Monetary Fund.

Because of this deficit, our politicians are in constant conflict with the providers of health care services. Some conflict is inevitable because the providers always wish to give the best possible service regardless of cost and the government agencies must attempt to control costs. But in our so-called free system, there exists a growing area of suspicion between the two parties and a mutual questioning of motives. The professionals do indeed fear the growth of "a terrible government bureaucracy [that would] prevent physicians from practicing quality care," and we are already experiencing rationed care. On the other hand, the politicians look at some of the larger incomes of members of the profession, paid not to the best physicians but to those who have learned to use the system to maximum advantage, and question whether the physicians are as idealistic as they say.

All this is unfortunate as the Canadian health insurance system was created in a spirit of cooperative endeavor between the various levels of government and the health professionals. But when the federal government, as a maneuver of political expediency, as well as misplaced idealism, passed the Canada Health Act of 1984, they not only removed all responsibility at the level of service from patients, but they also prevented the various provinces from experimenting with their own methods of controlling costs.

No money can now be charged by physicians at the level of service, or by the hospitals for such things as housekeeping or food, or for emergency services. The invisible police officer of restraint has gone, and the system is open to overuse and abuse. Those of us who work within the system can see this day in and day out. But it is denied or ignored by the politicians, not because they are unaware or stupid but because they are caught in a trap of their own making. Once a benefit is given to the electorate in a system of universal equal suffrage, it is politically impossible to take it away.

If at the same time the government is encouraging a policy of low taxation to stimulate the economy, then there can only be increasing national deficit financing.

It is for this reason that despite the excellence of our health service and despite the definite advantages that Grumbach's article describes, we would plead with our good neighbors to the south that should they embark on universal health insurance, they make certain of two essential preexisting conditions. The first is that all fiscal restraints are put in at the start of the plan, as it is very hard to put them in afterwards. The second is that there must be a mutually agreeable arrangement between the payers and providers of service as to how the schedule of benefits can be adjusted fairly up and down over the years to come.

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The Role of Echocardiography in Managing Cardiac Emboli

THE EXCELLENT REVIEW ARTICLE by John Stratton, MD, focuses on emboli from the heart as a result of nonvalvular atrial fibrillation or myocardial infarction. These two sources have assumed prominence as causes of emboli from the heart.

Left ventricular thrombi are undoubtedly the source of emboli in the setting of acute myocardial infarction. Two-dimensional echocardiography offers multiple advantages over other imaging techniques in thrombus detection. The sensitivity and specificity of two-dimensional echocardiography are equal to or better than all other modalities in thrombus detection. The test gives additional information

about left and right ventricular function, regional wall motion abnormalities, and other complications of myocardial infarction. The test can be safely and quickly done in a serial manner if necessary. Apical two-chamber and four-chamber views are generally all that are needed for left ventricular thrombus detection.

As Stratton points out, the decision about the use of anticoagulation is more often based on electrocardiographic findings. Patients with a transmural anterior wall infarction are a high-risk group for left ventricular thrombus formation. As many as 30% of these patients will form thrombi in contrast to the 2% or less incidence found in other groups.[1,2] As many as 20% to 30% of patients with left ventricular thrombus will have emboli.[3] As summarized in this review, full-dose anticoagulation is probably beneficial in reducing embolic events. Its benefit in preventing thrombus formation is less clear. Treatment with low-dose heparin and antiplatelet agents would appear to be ineffective in reducing embolic events or thrombus formation.[4] Based on presently available data, the benefits of full-dose anticoagulation with heparin followed by sodium warfarin therapy for several months would clearly appear to outweigh the risks of such treatment in most patients with anterior infarctions.

Two-dimensional echocardiography is the diagnostic imaging technique of choice, but it plays a more limited role in the decision as to whether or not to anticoagulate a particular patient. False-negative and false-positive studies occur in as many as 10% of patients.[5] A greater limitation of the technique is the variability in the timing of thrombus formation and embolization. Only about half of left ventricular thrombi form within 48 hours of an infarction.[1] Although almost all are formed by day 7, a significant percentage of the embolic events may occur within the first week following infarction.[2] Near-daily echocardiograms would then theoretically be required to use this technique to decide whether to institute anticoagulant therapy.

We would use two-dimensional echocardiography to determine the need for anticoagulation in those situations in which a relative contraindication to the use of anticoagulants exists. In these cases, the benefit-to-risk ratio may be substantially less. If a left ventricular thrombus is noted, we would proceed with anticoagulation. An apical wall motion abnormality is a sine qua non for thrombus formation. If the apex moves normally, anticoagulant therapy can be withheld. If apical dyskinesia, hypokinesia, or akinesia is present, but no thrombus is noted, we would withhold anticoagulant therapy but repeat the study in a few days to reduce the risk of "missing" a left ventricular thrombus.

As outlined in this review article, the benefits of anticoagulation in the setting of chronic left ventricular thrombus are less clearly defined. This issue arises frequently with the common use of two-dimensional echocardiography in patients with ischemic heart disease. Until further data are forthcoming, we would concur with the recommendation to withhold the routine anticoagulation of patients with chronic left ventricular thrombi. In the overwhelming majority of such patients, the thrombi are well endothelialized and of a much lower embolic risk than those in patients with an acute myocardial infarction.

Atrial fibrillation in the absence of mitral valve disease has now been shown to have a strong association with strokes. The Framingham data cited in the review article establish such an association.[6] Whether these strokes are secondary to a cardiac source, or whether long-term warfarin therapy would reduce the incidence of these strokes, is unclear.

The group of patients with nonvalvular atrial fibrillation is heterogeneous. Only in certain groups, such as those with dilated and hypertrophic cardiomyopathy, would long-term warfarin therapy appear to be indicated at the present time. This recommendation is based on the high embolic risk without such intervention. In most of the other groups, including those with ischemic heart disease, the benefits of long-term warfarin therapy have yet to be defined. In patients younger than 60 years with lone atrial fibrillation, warfarin therapy would not appear to be necessary.[7]

In contrast to the situation with left ventricular thrombi, two-dimensional echocardiography has a poor sensitivity for the detection of left atrial thrombi. This technique cannot be used to exclude embolization risk. Smokelike echoes detected in the left atrium with high-frequency transducers may be a marker for stagnant blood flow and left atrial thrombus formation.[8] Transesophageal echocardiography holds promise in the detection of left atrial thrombi and smokelike echoes.

Anticoagulation is currently recommended for three weeks before and four weeks after elective cardioversion from atrial fibrillation. This would apply to any patient with atrial fibrillation of more than two to three days' duration. This recommendation should apply to medical as well as electrical cardioversion attempts.

Lower dose warfarin therapy (using rabbit brain thromboplastin reagent) to keep the prothrombin time 1.2 to 1.5 times the control may be all that is necessary to prevent emboli from the heart in the setting of left ventricular thrombus or nonvalvular atrial fibrillation.[9] Further study is needed to confirm this recommendation. If confirmed, this "lower dose" warfarin therapy might be more commonly employed and, it is hoped, lower the risk of hemorrhagic complications.

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Case Reports

Primary Sternal Osteomyelitis

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STERNAL OSTEOMYELITIS has become more common in the past two decades largely related to the increased frequency of coronary artery bypass grafting and intravenous drug abuse. Sternal osteomyelitis as a complication of sternotomy is referred to as secondary sternal osteomyelitis; primary sternal osteomyelitis has no contiguous focus of infection. Contemporary cases of primary sternal osteomyelitis occur most commonly in intravenous drug abusers.[1] Primary sternal osteomyelitis remains a rarity with only 55 cases reported in the literature.[2] We report two cases of primary sternal osteomyelitis in patients with no apparent risk factors.

Report of Cases

Case 1

The patient, a 72-year-old man with non-insulin-dependent diabetes mellitus, was admitted for evaluation of an enlarging anterior chest wall mass. The patient had noted fullness in the left chest wall for a year before admission. Three weeks before admission, he had had sharp anterior chest pain that was precipitated when he arose from a sitting position or coughed. He also noted night sweats and dampness over the sternum. He said he did not have hemoptysis, dyspnea, dysphagia, anorexia, fevers, chills, or weight loss. He had not recently had an operation or trauma to the chest but did recall that a splinter of wood had lodged in the area near the lesion ten years previously.

On physical examination, the patient was afebrile but had a large—12 by 8 cm—wedge-shaped, erythematous, indurated mass over the anterior chest wall that protruded to the left of the midline. A chest roentgenogram revealed an osteolytic lesion of the sternum (Figure 1). On computed tomography there was destruction of the manubrium and adjacent ribs with soft tissue swelling extending into the anterior mediastinum (Figure 2). The results of laboratory tests included a leukocyte count of 12.4×10^9 per liter (12,400 per μl) and an erythrocyte sedimentation rate of 120 mm per hour.

An incisional biopsy of the sternum was done and a histopathologic examination showed chronic inflammation. Culture of the biopsy grew *Staphylococcus aureus* sensitive to vancomycin hydrochloride, oxacillin sodium, and cephalothin sodium. A regimen of nafcillin sodium, 8 to 10 grams per day given intravenously, was initiated but stopped after 14 days due to a skin rash. The suspicion for carcinoma or sarcoma was high, and because the initial biopsy did not show malignancy, a second biopsy was done. Further local debridement was done at the time of biopsy, but no costal cartilages were removed. The biopsy specimen again did not show a neoplasm. A Penrose drain was placed, but the wound was closed with mattress sutures. A Hickman catheter was placed, and intravenous cefazolin sodium was administered at home for a period of three months. The erythrocyte sedimentation rate dropped to 15 mm per hour after four months, and a repeat computed tomography examination eight months later revealed a decrease in the size of the chest mass (Figure 2). Currently, two years later, the patient remains asymptomatic.

Case 2

Our second patient, a 59-year-old man with peripheral vascular disease, had been placed on sodium warfarin therapy following a femoral-to-popliteal artery bypass operation. In mid-November 1983, he had chest wall pain that had developed during a hospital admission for a right lower lobe pneumonia. The patient was treated as an outpatient with ibuprofen and acetaminophen given for presumed costochondritis. A month later, itching and redness developed over the sternal area directly beneath a nickel-plated necklace recently given to him to monitor the warfarin therapy. An erythematous skin rash was noted in the sternal area, and radiographs revealed the persistence of congenital ossified centers of the sternum (Figure 3). In January of 1984, an area of fluctuance was noted beneath the erythema, and a percutaneous aspirate from this area grew *S aureus.* Tomograms were suggestive of an osteolytic lesion (Figure 4). Surgical exploration was done for the purpose of biopsy, culture, and debridement. Under general anesthesia, the body of the sternum underwent curettement, leaving the posterior plate intact. The wound was then packed with iodoform gauze. Three months later the patient was noted to have a sinus tract at the site of the old surgical scar, and this was explored under general anesthesia. The sternum again was curetted and packed with iodoform gauze. Because of allergic reactions to multiple antibiotics, the patient received several different drug regimens including neomycin, nafcillin, and cephapirin sodium over a period of six weeks. An eight-week course of erythromycin followed the parenteral use of antibiotics. *Staphylococcus aureus* was grown from the biopsy specimens of both surgical procedures. Four years later the patient remains infection free.

Discussion

Primary sternal osteomyelitis, once a rare disorder, has become more common today with the increased prevalence of intravenous drug abuse. The most common bacterial cause of primary sternal osteomyelitis in intravenous drug abusers is *Pseudomonas aeruginosa,* although the most common overall is *S aureus.*[2-4] *S aureus* is also the most common pathogen in secondary sternal osteomyelitis. It is interesting that *Mycobacterium tuberculosis* has become a rare cause of sternal osteomyelitis since 1952.[5]

Vaughn's review of sternal osteomyelitis in 1918 indicated that only 13 cases had been reported before 1910,[6] and all were in the German literature.[7] Wilensky and Samuels (1926) reported 24 cases of primary sternal osteomyelitis,[8] but because several of the cases described were characterized by generalized sepsis, we have excluded these in our listing

(Gill EA Jr, Stevens DL: Primary sternal osteomyelitis. West J Med 1989 Aug; 151:199-203)

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of the total number of cases with primary sternal osteomyelitis (Table 1).[1-13] In their series, the mortality rate was 27%, which is higher than in any other series.[8] Many of their patients died of septic shock. Since the 1926 review, an additional 30 cases have been reported in international medical journals, bringing the total to 55 cases.

Table 2 compares cases of primary and secondary osteomyelitis both in terms of treatment and complications. Note that secondary sternal osteomyelitis was not described in the preantibiotic era. Since the introduction of the coronary artery bypass procedure, however, secondary osteomyelitis has become a well-known complication. Culliford and coworkers defined predisposing risk factors for poststernotomy osteomyelitis[15]: a prolonged perfusion time, excessive postoperative bleeding, a depressed cardiac output, and reexploration for the control of hemorrhage. In addition, internal mammary artery bypass grafts have increased the risk of sternotomy infection as compared with vein grafts. In fact, the overall infection rate of 1.5% climbed to 2.3% with the use of one internal mammary artery bypass and to 8.5% with bilateral internal mammary artery grafts.

Primary sternal osteomyelitis presents with anterior sternal pain, redness, tenderness, and swelling. When evaluating a case of chest wall pain or a mass in the sternal area, it is most important to consider sternal osteomyelitis in the differential diagnosis. Delayed diagnosis and inappropriate treatment are common in this illness. The differential diagnosis of primary sternal osteomyelitis is broad and should include cellulitis, soft tissue abscess, benign soft tissue tumors, and soft tissue or bony sarcoma. Fibrosarcoma is the most common soft tissue sarcoma. Bone sarcomas are rare, the most common being osteosarcoma and Ewing's sarcoma,

Figure 1.—A lateral chest x-ray film shows soft tissue swelling and destruction of the sternum **(arrows)** in patient 1.

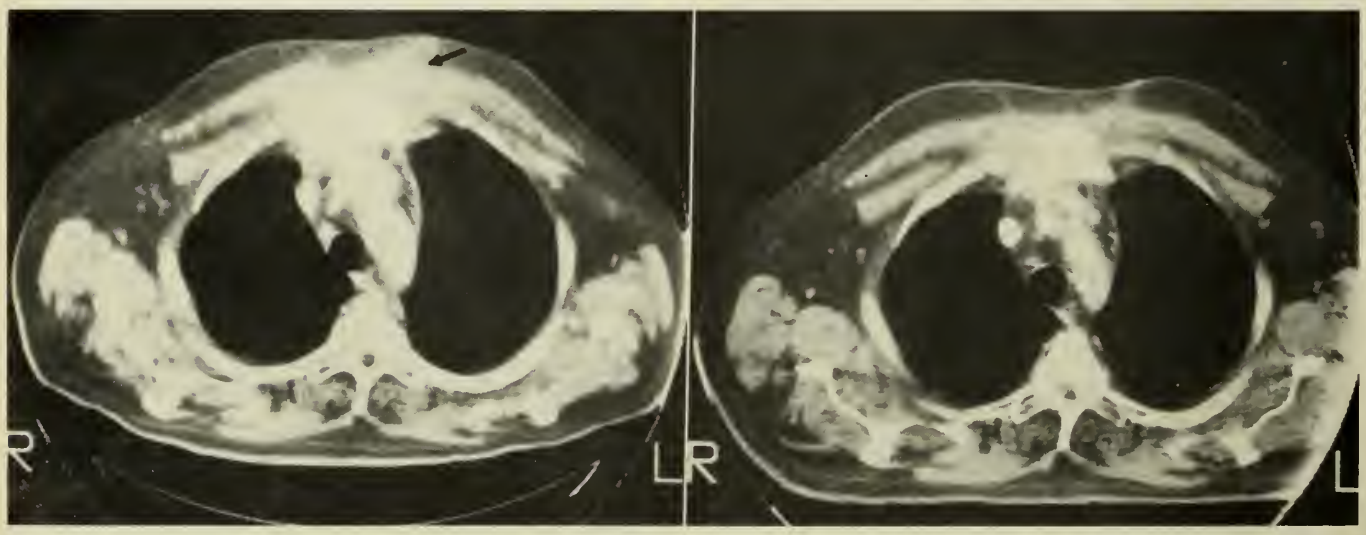

Figure 2.—Chest computed tomography in patient 1 shows, **left**, sternal destruction and inflammatory response extending through bone and soft tissue to the chest wall surface **(arrow). Right,** 9 months later, after surgical debridement and antibiotic therapy, the destructive process of the sternum is nearly absent.

TABLE 1.—*Reported Cases of Primary Sternal Osteomyelitis (N=55)*

Reported Case	Author, Year	Age, yr	Sex	Source of Bacteria	Organism	Surgical Therapy	Underlying Disease	Trauma	Outcome
1	Wilensky and Samuels, 1926[8]	24	♂	Typhoid	Unknown	Debridement	...	No	Survived
2		35	♀	Sternum	*Salmonella paratyphi*	Debridement	...	No	Survived
3		24	♂	Sternum	Unknown	Radical resection*	...	Yes	Survived
4		8	♂	Sternum	*Staph aureus*	Debridement	...	Yes	Survived
5	Drews, 1910[7]	Young†	..	Sternum	*Staph aureus*	Debridement	...	No	Survived
6-18	Drews, 1910[7]‡								
19	Solomon, 1926§	Young†	..	Pneumonia	Unknown	Debridement	...	No	Died
20	Sick, 1926§	40	♂	Pneumonia	Unknown	Debridement	...	No	Died
21		16	♂	General infection‖	...	...	...	No	Died
22		15	♀	Sternum	Unknown	...	...	No	Survived
23		21	♂	Sternum	Unknown	...	...	No	Survived
24	Muhlein, 1926§	..	..	Lung	Unknown	...	Splenic tumor	...	Died
25	Batut, 1926§	22	♂	Sternum	*Salmonella typhi*	Debridement	Unknown	...	Survived
26	Vaughn, 1918[6]	26	♂	Sternum	Unknown	Debridement	...	Yes	Survived
27	Peloquin, 1926§	..	..	Sternum	...	4 operations	...	No	Died
28	Bidwell, 1926§	..	..	Liver	Unknown	Debridement	Liver abscess	No	Died
29	Koch, 1926§	30	♂	Pneumonia	...	Radical resection	...	No	Survived
30	Janz, 1926§	21	♂	Pneumonia	Unknown	Debridement	...	No	Survived
31	Busch, 1926§	18	♂	Sternum	Unknown	Radical resection	...	No	Survived
32	Maier, 1947[9]	19	♀	Pneumonia	*Streptococcus* sp	Debridement	...	No	Died
33	Brown, 1952[10]	19	♂	Sternum	?*Mycobacterium tuberculosis*	Debridement	...	No	Survived
34		41	♂	Sternum	*M tuberculosis*	Debridement	...	No	Survived
35		28	♂	Sternum	*M tuberculosis*	Several	...	No	Survived
36	Vellacott, 1952[11]	26	♂	Sternum	*Staph aureus*	Debridement	Unknown	Yes	Survived
37	Biesecker, 1973[12]	21	♂	Sternum	*Staph aureus*	Debridement	...	No	Survived
38		2½	♂	Sternum	Gram-negative	Debridement	...	No	Survived
39	Mir-Sepasi et al, 1975[1]	22	♂	Sternum	*Pseudomonas aeruginosa*	Radical resection	IV drug abuse	No	Survived
40		24	♂	Sternum	*P aeruginosa*	Debridement	IV drug abuse	No	Survived
41		21	♂	Sternum	*P aeruginosa*	Debridement	IV drug abuse	No	Survived
42		24	♀	Sternum	*P aeruginosa*	Debridement	IV drug abuse	No	Survived
43	Enat et al, 1979[13]	47	♂	Sternum	*Staph aureus*	...	...	CPR	Survived
44-50	Jara et al, 1979[4]¶								
51	Sant, 1979[3]	28	♀	Sternum	*Staph aureus*	...	...	...	Survived
52	Kelly and Chetty, 1985[2]	40	♀	GI tract	Gram-negative	...	...	...	Survived
53	Richter, 1983[14]	..	..	Sternum	*M tuberculosis*	...	...	...	Survived
54	Watts et al, 1987[5]	40	♂	Sternum	*M tuberculosis*	Debridement	...	No	Survived
55		49	♂	Sternum	*M tuberculosis*	...	...	No	Survived

CPR=cardiopulmonary resuscitation, GI=gastrointestinal, IV=intravenous, *Staph*=*Staphylococcus*

*Radical resection was defined as complete resection of the sternum with additional reconstruction.
†A minimal description of patients was given, with age described only as young.
‡Cases 6-18: Drews cited 13 cases from the German language literature.
§All of these cases were described by Wilensky and Samuels, 1926.[8]
‖This may well have been a case of generalized sepsis.
¶Cases 44-50: 7 patients (1 woman, 6 men), all intravenous drug abusers, were treated with debridement and all survived. The causal organism in 4 was *Pseudomonas aeruginosa*, in 2 was *Staphylococcus aureus*, and in the 7th was undetermined. The ages and sources of bacteria were not given.

TABLE 2.—*Primary Versus Secondary Sternal Osteomyelitis*

Feature	Sternal Osteomyelitis: Primary	Sternal Osteomyelitis: Secondary
Risk factors	Trauma; ?pneumonia, ?diabetes	Internal mammary artery bypass grafting; prolonged time on heart-lung bypass; sternal massage for CPR after an operation; prolonged low cardiac output state after a bypass procedure; excessive bleeding; history of reexploration for control of bleeding
Complications	Sepsis	Wire, saphenous vein bypass valve, and mediastinal infection; sepsis; sternal erosion
Mortality rate	Preantibiotic era, 19% Postantibiotic era, 3%	10% all cases in postantibiotic era
Management	Antibiotics with or without surgical therapy	Antibiotics plus reconstructive operations in most cases—left to heal open
Organism	*Staphylococcus aureus, Pseudomonas aeruginosa*	*Staphylococcus aureus, Klebsiella pneumoniae, Candida albicans*

CPR=cardiopulmonary resuscitation

Figure 3.—A plain lateral chest film of patient 2 shows midsternal hypertrophy and a questionable accessory joint **(arrows).**

Figure 4.—A tomogram of the sternum shows the destructive process of the sternal osteomyelitis **(arrows).**

both mainly pediatric tumors. Sarcoma is important to consider because a biopsy may facilitate a contiguous spread, and a complete surgical resection is necessary for cure in many cases.

The diagnosis of sternal osteomyelitis requires a bone biopsy. Helpful radiologic studies include computed tomography, a technetium Tc 99m pyrophosphate bone scan, and scans using gallium citrate Ga 67 and indium In 111. All of the nuclear medicine scans lack specificity and are perhaps best suited for follow-up examinations. Smith and associates, however, have advocated the use of gallium ^{67}Ga scanning as more specific than technetium ^{99m}Tc scanning.[16] It is unclear from their report whether or not the ^{99m}Tc scans were multiphasic.[16] We found plain and computed tomography to be the most useful in the diagnosis and follow-up of our patients. Although no studies exist supporting its use in this illness, magnetic resonance imaging has been useful in some types of osteomyelitis, especially in patients with Pott's disease.[17]

The treatment of secondary sternal osteomyelitis requires more aggressive debridement than does the primary form. Hence, most cardiothoracic surgeons advocate extensive surgical intervention with some reconstruction in most cases. Johnson and colleagues have recommended total sternectomy and removal of associated cartilage, with reconstruction accomplished using bilateral pectoralis major myocutaneous flaps.[18]

While some debridement is often necessary in primary sternal osteomyelitis, a few cases ($<10\%$) will resolve with antibiotic therapy alone. The extent of sternal debridement has been reviewed in a noncontrolled, nonprospective manner by two sets of authors. Mir-Sepasi and co-workers suggest removing most of the sternum but recommend leaving the posterior periosteum intact.[1] Such a conservative approach was curative in both of our cases, but each required a second operation.

Conclusions

We have presented two cases of primary sternal osteomyelitis, making the total of reported cases 57. Each patient had significant underlying illness: diabetes mellitus and peripheral vascular disease, respectively. Diabetes could certainly be postulated a risk factor for this disease. Case 1 also was unusual in that there was a preexisting history of a foreign body more than ten years before the patient was first seen. Our cases were more typical of the older cases in the literature in that there was no history of intravenous drug abuse. We also report what we think is the first case of this illness treated on an outpatient basis with intravenous antibiotics through a Hickman catheter. Hence, we have defined an approach to this illness combining appropriate diagnostic studies, limited surgical intervention, and appropriate antimicrobial therapy.

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Metastatic Crohn's Disease

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GRANULOMATOUS LESIONS OF THE SKIN not attributable to a known foreign body reaction or infectious agents are often presumed to be sarcoidosis, a disease of exclusion. We report the case of a patient initially thought to have cutaneous sarcoidosis, who on further investigation was determined to have "metastatic" Crohn's disease.

Report of a Case

The patient, a 62-year-old man, first consulted our dermatology service for evaluation of an erythematous, scaly, nummular patch on his left lower leg that had been present for about two months.

Further history indicated that six months before he noted the lesion, he had been ill with malaise, diarrhea, vomiting, and a 9-kg (20-lb) weight loss. He was admitted to hospital and underwent an extensive evaluation, including radiographic studies that revealed tumors in the antrum of the stomach and terminal ileum (Figure 1). These were initially considered to be consistent with adenocarcinoma, but an endoscopic biopsy of the gastric lesion showed many noncaseating granulomata. No other systemic illnesses or abnormalities were identified at that time. A diagnosis of Crohn's disease was made after tuberculosis and other causes for the granulomata were ruled out. He was treated with a regimen of prednisone, 30 mg a day, with complete resolution of all gastrointestinal symptoms. The patient had been completely weaned off prednisone at the time of being seen by us.

About two months after the prednisone therapy was discontinued, he was examined in the dermatology clinic because of mild erythema and scaling that had developed on both legs. Several potassium hydroxide preparations were negative, and the patient was initially treated with mid-strength topical steroids with no apparent response. The lesions progressed, and eventually thickened, indurated plaques developed with sharply marginated ulcerations and crusting (Figure 2).

Several skin biopsies revealed sarcoidal granulomas with few giant cells and little coagulation necrosis (Figure 3). Special stains and cultures were negative for deep fungi, acid-fast bacteria, and spirochetes. No foreign body material was identified by polarization. A diagnosis of sarcoidosis was initially made, and a complete evaluation for systemic involvement was embarked on. All results were normal. The patient had no adenopathy. A chest x-ray film showed no hilar

Figure 1.—A barium-enhanced radiographic examination of the intestine reveals cuffing of the terminal ileum (**arrows**) characteristic of Crohn's disease.

Figure 2.—The initial skin findings consisted of dermatitis and scaling of the legs within which there is ulceration and crusting.

(McGillis ST, Huntley AC: Metastatic Crohn's disease. West J Med 1989 Aug; 151:203-205)

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adenopathy nor evidence of tuberculosis. Angiotensin-converting enzyme levels were within normal limits. On routine laboratory studies, all values including serum calcium levels were normal. An ophthalmologic evaluation revealed no ocular lesions. Serum immunoglobulin levels were also normal. A repeat gastroendoscopy showed no recurrence of the mucosal lesions. No other cutaneous lesions were noted at that time.

Because of the established diagnosis of Crohn's disease involving his bowel and the lack of involvement in other target organs typical for sarcoidosis, his cutaneous reaction seemed to best fit into the category of "metastatic" Crohn's disease. He was treated with a regimen of oral prednisone with gradual resolution of the skin lesions (Figures 4 and 5). Following resolution of the leg lesions, the prednisone therapy was again discontinued. Over a period of months, histologically and clinically similar new skin lesions developed on his back. Prednisone was readministered with an excellent response, and he has been lesion-free for more than a year.

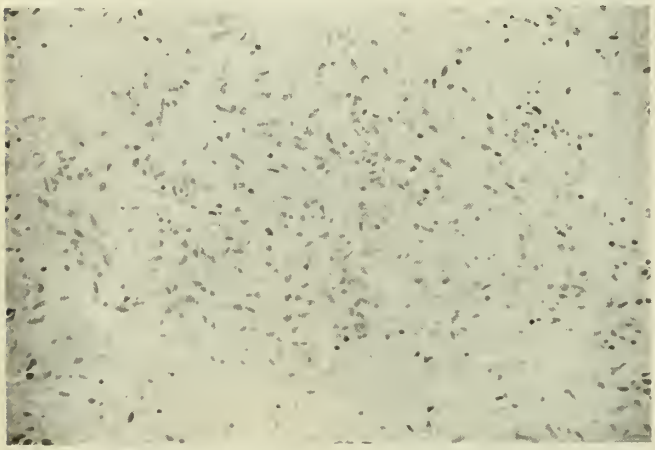

Figure 3.—A high-power field of the reticular dermis from the skin biopsy of the patient's leg shows a sarcoidal granuloma (hematoxylin and eosin, × 400).

Discussion

This case is an example of metastatic Crohn's disease and shows some of the difficulty in differentiating between Crohn's disease and sarcoidosis, two diseases of diagnostic exclusion that can have similar clinical and histologic involvement of the skin. Differentiation is based primarily on the pattern of extracutaneous involvement.

Our initial working diagnosis was cutaneous sarcoidosis. His skin findings were similar to those recently reported in two other patients with sarcoidosis,[1,2] but in both those patients systemic evidence of sarcoid was well documented; in our patient, the only other disorder was of his gastrointestinal tract. When making a diagnosis of sarcoidosis in the skin, involvement of other target locations is sought. Sarcoidosis most commonly involves the lungs (90%), followed by skin (30%), lymph nodes (27%), and eyes (27%). Gastrointestinal involvement is distinctly rare for this disease.[3] Based on the results of an endoscopic biopsy, his gastrointestinal disorder was diagnosed as Crohn's disease. The skin lesions are also clinically and histologically consistent with this process.

Figure 4.—Six weeks after prednisone therapy was started for his skin problem, the patient's dermatitis is moderately resolved and the punched-out nature of the ulcers is more clearly shown.

Figure 5.—Substantial improvement of the skin of the patient's legs is seen after about three months of prednisone therapy.

In fact, it is not uncommon for Crohn's disease to show extraintestinal involvement: as many as 44% of patients have skin findings.[4] Most of these lesions occur in close proximity to the gastrointestinal tract and thus are thought to be due to direct extension. These include perineal ulceration, fistula formation, and granulomatous peristomal lesions. Patients with large bowel and colon involvement are most likely to have skin disease.

So-called metastatic Crohn's disease refers to extraintestinal involvement not due to direct extension of the disease. Of 15 reported cases of metastatic Crohn's disease, specific skin lesions have included nodules, plaques with and without ulceration, ulcerated patches, lichenoid papules, intertriginous ulcerations, erysipelas-like eruptions, and vulval swelling.[5,6] There does not seem to be a relationship between bowel activity and cutaneous disease.[7] Granulomatous ulceration of the extremities, similar to our patient's initial cutaneous presentation, has been reported.[8]

Nonspecific cutaneous lesions may also occur in Crohn's disease. Such lesions include oral mucosal lesions such as aphthous ulcers and a mucosal cobblestone pattern and those lesions that occur as the result of nutritional deficiency, such as acrodermatitis enteropathica.[9] Other skin reactions noted in Crohn's disease include pyoderma gangrenosum, erythema nodosum, erythema multiforme, epidermolysis bullosa acquisita, finger clubbing, and palmar erythema.[10] Like sarcoidosis, cutaneous Crohn's disease occurs in many forms.

On histologic examination, metastatic Crohn's disease shows dermal or subcutaneous noncaseating granulomas for which infections, sarcoid, foreign body granulomas, and tuberculosis have been ruled out.

This case illustrates the important point that sarcoidosis and Crohn's disease may have similar cutaneous findings. Crohn's disease should be added to the list of diseases to be excluded in patients with cutaneous sarcoidal granulomas, especially in those patients with gastrointestinal complaints.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

A Safer Blood Supply

To THE EDITOR: The editorial by Dr Paul Bunn in the May issue calls attention to the desirability of testing the blood supply for the presence of HTLV-I infection.[1]

Your readers would probably appreciate knowing that HTLV-I testing has been part of the routine for insuring the safety of the blood supply for the past several months for all blood issued in the United States.

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REFERENCE

1. Bunn PA Jr: HTLV-I-associated diseases (Editorial). West J Med 1989; 150:578-579

The Increased Rate of Fractures of the Hip and Spine in Alzheimer's Patients

To THE EDITOR: It was suspected that patients with Alzheimer's disease would experience an increased rate of fractures of the hip and spine.

Method

A computer printout of women patients over the age of 60 with either a primary or secondary diagnosis of Alzheimer's disease was obtained. The medical records of these patients were then reviewed. There were 20 patients in this study with Alzheimer's disease. For a control, the records of 60 patients who were matched for age, race, and sex were similarly reviewed.

Results

In the 20 patients with Alzheimer's disease, 10 (50%) were found who had fractures of either the hip or spine. Of the 60 persons in the control group, 12 (20%) had fractures. A P value was obtained of less than .001.

Discussion

It appears that there is a significant correlation between Alzheimer's disease and fractures of the hip and spine as compared with controls. This correlates with results of a 1986 study by Buchner and Larson.[1] Patients with Alzheimer's disease need to be protected. The reason for this association may be more significant. This relationship can have only two logical explanations. Either Alzheimer's disease caused an increased rate of fractures, or osteoporosis, which predisposes to this type of fracture, and Alzheimer's disease have a common origin. In support of the former explanation, patients with Alzheimer's disease could have a poorer diet, less exercise, or otherwise have increased rates of osteoporosis.[2,3] They may simply fall more frequently. If Alzheimer's disease increased the frequency of fractures or the rate of the development of osteoporosis, these patients must sustain the fractures at a younger age than the control group with the same fractures. To determine if this was in fact the case, we compared the average ages of the Alzheimer's group who had fractures of the hip and spine with the control group, who had similar fractures. The average ages were 77.6 and 77.1, respectively. There was no significant difference. Alzheimer's disease does not appear to have increased the fracture rate or accelerated the development of osteoporosis. These observations are not inconsistent with the hypothesis that Alzheimer's disease and osteoporosis are derived from a mutual agent.

If this conclusion is correct, it follows that the therapy for osteoporosis should be efficacious in treating Alzheimer's disease.[4] Aside from the theoretical explanation of the etiology, treating Alzheimer's patients for osteoporosis can be justified on the basis of the association with fractures.

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Lyme Disease in Northern California

To THE EDITOR: A recent article in the journal indicated that the vector of Lyme disease inhabits the entire West Coast.[1] In northern California fear of Lyme disease is rampant because of an increased number of case reports and the drama of the news media. People visualize infected ticks perched on bushes and grass waiting to infect all passersby. As this disease becomes more widely recognized throughout the West, fear of Lyme disease will spread. This fear is quite false based on current data, medical literature, and expert opinion. As physicians we must educate our patients about this disease and quiet their fears.

The offending spirochete, *Borrelia burgdorferi,* is transmitted in the West by the deer tick, *Ixodes (Ixodes) pacificus.* It occurs year round, with a major peak in summer and a second lesser peak in winter. Lyme disease occurs in stages of active and silent disease. The illness usually begins with a skin rash, erythema chronicum migrans, and may be followed by cardiac, neurologic, or joint problems. Laboratory tests may be helpful but are not standardized or totally reli-

able for the diagnosis. Antibiotic treatment is beneficial, particularly in the early phases.

Fear of Lyme disease is unwarranted in northern California as well as the rest of the state because only 1% to 2% of the ticks are infected. This statewide percentage has been stable for the past five years. These figures come from the California State Department of Health and University of California experts using the most accurate, painstaking individual tick testing methods (Robert S. Lane, PhD, University of California, Berkeley, oral communication, July 1989).

This low infection rate is in contrast to that in the East where in some areas 30% to 80% of ticks are infected. In other areas, the infection rate has grown rapidly in recent years. The reason for this difference is that the life cycle of the eastern tick involves warm-blooded mice that carry the infection. Our western tick cycle involves cold-blooded lizards that do not contract or carry the organism. *I pacificus* inhabits the entire coast range and eastern Sierras. Because of this low infection rate experts do not recommend routine prophylactic treatment of tick bites in the West.

Some simple tips can lessen our patients' risk of this disease:

- Avoid tick bites. When in areas where there may be ticks, tuck in shirt at the waist, and tuck trousers into socks. Light clothing can show ticks, and a repellent using diethyltoluamide (deet) on clothing may be helpful.
- Remove ticks promptly. Check all family members promptly and thoroughly, including the hairline, underarms, navel, groin, and behind the ears. Ticks like shade and humidity, and they frequently scout around for many hours. Prompt removal can lower risk because it generally takes at least 24 hours of feeding to transmit the organism. An experimental study of infected eastern ticks on rodents found only 7% infected after 24 hours of feeding, 37% infected at 48 hours, and 93% at 72 hours.[2] Similar studies will soon be underway on the Western tick vector. Results may differ, however, because only 5% of infected Eastern ticks carry the spirochete systemically outside their midgut, while 30% to 40% of infected Western ticks are systemically infected. This may explain Lyme disease occurring from briefer tick feeding in California.
- Remove ticks properly. Heated matches, vaseline, nail polish, alcohol, and the like should not be used. In fact they may increase risk by stimulating the tick to regurgitate infected stomach contents. The best method is to use tweezers or covered fingers. Grasp the tick as close to the skin as possible and not by the body. Pull straight out—without twisting—at 90° with steady traction. If the "pincers" break off there is no great risk of infection because the Lyme spirochete is in the tick's stomach, which has been removed. Theoretically, the spirochete can go through the skin, so do not squash the tick. Wash fingers afterwards. Always use tweezers when removing large numbers of ticks from a dog. (Animals also can contract Lyme disease.)
- Save the tick. Check with a physician for possible identification.
- Watch for the erythema migrans rash. This early stage of Lyme disease can occur with no remembered tick bite. Particularly in spring and summer, tiny speck-like nymphal ticks occur. They may feed and drop off without a trace. Any red, circular, or oval enlarging rash with or without a central bull's-eye clearing should be reported promptly to a physician. Furthermore, a flu-like illness within a few weeks of a tick bite even without a rash warrants a physician's attention. Lyme disease may occur without the rash. Early antibiotic treatment is the best insurance to prevent late complications of Lyme disease.

The Northern California Lyme Disease Study is a surveillance study as well as a physician and patient education study of Lyme disease. We make available a patient education handout that includes tips on preventing tick bites and properly removing ticks. This handout can be reproduced and given to our many anxious patients. We also have pictures of erythema chronicum migrans. We would be happy to send these to all who are interested upon receipt of a self-addressed, stamped envelope.

Widespread preventive education can turn the tide and diminish Lyme disease in the near future. In the meantime, with simple precautions our patients can enjoy an outdoor summer without fear of Lyme disease.

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Managing Hypercholesterolemia

To THE EDITOR: Robert Baron should be commended for a well-written, thorough, and up-to-date article on the management of hypercholesterolemia.[1] Unfortunately, his review is far from complete as a "primary care perspective" and fails to address issues of importance to the true day-to-day care of patients.

Most important, Dr Baron does not comment on the issue of age. Should a 78-year-old woman obtain a cholesterol level every five years? Should such a patient be treated for a level of 240 or greater? Should she drastically alter a diet of many years?

Other questions are ignored as well. At what age should cholesterol levels first be drawn? Is there a problem extrapolating data drawn exclusively from men (ages 30 to 65) to a recommendation for women?

The unfortunate reality in primary care is that many of our patients who are most concerned about the cholesterol issue are over 70 years of age. Until more is known about this age group, it is hardly warranted to conclude a cholesterol review with the lead-in: "All adult patients should. . . ."

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* * *

To THE EDITOR: We applaud Dr Robert B. Baron for his excellent discussion of the management of hypercholesterolemia.[1] His article is succinct, comprehensive, and of obvious value to primary care physicians.

We would like to supplement his comments in regard to the role of physicians in assisting patients to change their

behaviors. The definition of health education that we have found most helpful is that behavior of physicians that assists patients in making positive health related decisions. One of the important implications of this definition is that the locus of control for making behavioral changes lies with the patient. It is the physician's role to facilitate this action.

The American Heart Association's Physicians Cholesterol Education Program[2] incorporates five important components of physician behavior that can facilitate change on the part of patients:

- Create an environment for learning
- Assess the needs of the patient
- Design a plan of action
- Implement the plan
- Evaluate outcomes

Since the Heart Association is currently sponsoring educational programs to acquaint physicians with new information on reducing risk factors for coronary artery disease and specifically cholesterol, we would suggest that physicians seek out the opportunity to participate in these workshops.

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Snake Oil

To THE EDITOR: The snake has been a part of Western medicine since the time of the ancient Sumerians, 4,000 years ago. Ningishzida, their god of healing, was draped with twin snakes, an emblem still in fashion in medical circles today. Snake was an ingredient of a famous theriaca used by Andromachus, physician to Nero, and of a theriaca of Galen, which was in use until the efforts of William Heberden to ban it in 18th century England. It was still quite popular in colonial America, however, and only in the past century have snake and snake oil become synonymous with quackery.

Another kind of oil has come into fashion recently: fish oil has been elevated to the front rank of medical therapeutics because of convincing clinical and laboratory research that documents effects on platelets, white blood cells, and blood vessel walls. Clinical benefits in treating inflammatory disorders, cardiovascular disease, and even cancers are now subjects of serious research. These effects are known to be related to the presence in fish oil of ω-3 essential fatty acids, which are precursors of prostaglandin hormones. It is well known that the biology of both plants and animals commonly adapts to cold temperature by producing more of the ω-3 unsaturated fatty acids with one more double bond than the ω-6 fatty acids.

Since snakes are cold-blooded animals, it seemed plausible to me that they might contain ω-3 essential fatty acids. Finding no listing of snake oil in the analytical tables, I sent three specimens of snake to a laboratory for analysis by chromatography and flame ionization (analysis by Dr George Miroff, Monroe Medical Laboratory, Southfields, New York). Table 1 shows the major fatty acids found in snake oil from Chinese snake oil purchased over the counter, subcutaneous fat of a black rattlesnake from southern California *(Crotalus viridis)*, and subcutaneous fat of a red rattlesnake from Arizona *(Crotalus tigris)*.

TABLE 1.—*Fatty Acid Fractions in Snake Oils, % Concentration*

	ω-3			ω-6			
Source	*ALA*	*EPA*	*DHA*	*LA*	*GLA*	*DGLA*	*ArA*
Chinese snake oil	0.001	19.6	0.001	4.4	0.001	0.001	2.4
Black rattlesnake .	1.4	4.1	0.1	9.7	0.7	2.8	4.7
Red rattlesnake . .	0.5	0.6	5.4	20.8	0.06	0.1	12.8

ALA=α-linolenic acid, ArA=arachidonic acid, DGLA=dihomo γ-linolenic acid, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, GLA=γ-linolenic acid, LA=linolenic acid

Chinese snake oil contains almost 20% eicosapentaenoic acid (EPA), about triple the concentration in the American rattlesnakes. I understand the Chinese product includes snake oil from water snakes that feed on fish. This almost certainly would increase the content of EPA in their tissues. In human subjects fed cod liver oil, there was a sevenfold increase of EPA in neutrophils and monocytes. It was also found that arachidonic and docosahexaenoic acids did not increase and that leukotrienes decreased; hence the inference that anti-inflammatory action was due to EPA and that it may work by inhibiting the leukotriene B_4-mediated output of neutrophils.[1]

As a concentrated source of EPA, snake oil is a credible anti-inflammatory agent and might indeed confer therapeutic benefits. Since essential fatty acids are known to absorb transdermally, it is not far-fetched to think that inflamed skin and joints could benefit by the actual anti-inflammatory action of locally applied oil just as the Chinese physicians and our medical quacks have claimed.

It is not unusual that an ancient remedy or a folk medicine turns out to have some merit. What is unusual is that this particular therapy, snake oil, has long been our favorite symbol of quackery. I find it humbling that the science of today invests the quackery of yesterday with new credibility. Perhaps our ancestors were wiser than we could appreciate when they wrapped a snake around the staff of Aesculapius.

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More on Dismemberment

To THE EDITOR: Your editorial, "On Dismemberment of the Corpus of Medicine," in the May issue[1] makes an extremely important point.

First of all, it is important to understand why this is happening, and Alvin Toffler has stated, "After 10,000 years of agrarian life, or 'first wave' civilization, we created a smoke-stack society, we and our grandparents, which was in fact based on mass production, mass distribution, mass education, mass entertainment, mass recreation, and mass destruction. The industrial revolution launched a 'second wave' of social transformation. Today we are feeling the impact of history's third great wave of change. And what is happening

today cannot be understood unless we recognize a process that I call 'demassification.' We're taking that mass society and we're differentiating it. We're breaking it up into more diverse and rapidly changing pieces."[2]

You have struck on the proper point when you say that the specialists are all splitting off as if they needed to protect their own incomes and their own turf, and this is dangerous. Why should neurosurgery, for example, with 0.9% of the patient population in the nation under its care, have a political representative in Washington?

This is multiplied by many other numbers by various specialties.

I have found the medical association in my state and the American Medical Association (AMA) to be as thoroughly representative of the interests of medicine as a whole as they can be. These organizations are not perfect, nor are they likely to become so as human institutions, but they are the best we have, they are democratic, and anyone who wants to give the time and produce the effort to succeed in these organizations can do so. It is my feeling that the state medical associations offer a very strong backdrop for the federation of the AMA, and all physicians who want to be represented can be. There is very little reason for anyone to complain about the decisions that "they" make, since the reason those people are making decisions is that "we" are not there to discuss the problems.

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Misleading Articles

To THE EDITOR: The Editors should be criticized for permitting misleading statements and impressions to be published in the journal. The articles in the March 1989 issue relating to "Low Back Pain Care"[1] and to "Physician Communication Skills"[2] are "poorly conceived but brilliantly executed." The article on low back pain purports to report the "differences in patients' evaluation of their care from family physicians and chiropractors." The article discusses the differences in perception of patients enrolled in a health maintenance organization (HMO) on the care they received from their HMO primary care physician and from chiropractors "in the community." Most "allopathic" physicians agree that the outcome or response to treatment of low back pain is dependent mainly on the general well-being of the patient and, unfortunately, on the balancing of the pain and disability with the secondary gains. To me, the differences of patients' evaluation of their care resulted more from the basic differences in the doctor-patient relationship. To the HMO physician, the patient with low back pain represented only another problem to solve; and to the non-HMO chiropractor, the patient represented a good source of income, with further income being dependent on how well he or she satisfied the wishes of the patient.

The article on physician communication skills really related to surgeons and anesthesiologists and to postoperative and postdelivery patients. The mean number of total claims "was 4.45." Of the contacted physicians, 68% and 77% "declined the invitation to participate." The participation rates of 26%, 29%, and 12% would make the data highly suspicious as to their reliability for surgeons and anesthesiologists, much less for physicians in general, to which the article supposedly relates. Although some of the conclusions that the authors made in this article are undoubtedly true, it would be erroneous to conclude from their data that the patient's sex or level of education has a great deal to do with whether the patient files a claim or not. Although most experts on malpractice liability do not explicitly state this, it seems to me that the prime factor for suing or not is the doctor-patient relationship. Most suits are filed because the patient (or relative) is unhappy or angry with the physician. Probably a minority of suits are filed because of gross mistakes by physicians (plus those suits urged on by overzealous attorneys).

I believe that it is the responsibility of an editor either to reject a manuscript that conveys a mistaken message or to require the authors to change the wording of their article, especially where their discussions and conclusions are not warranted by their data. Last, I believe the subject matter of the two reports is vital to the medical profession. I would laud and encourage the editors to continue.

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Familial Thyrotoxic Periodic Paralysis

To THE EDITOR: In the April 1989 issue, Kufs and colleagues reported on two Filipino-Chinese brothers who were simultaneously found to have Graves' disease presenting as periodic paralysis and whose father had the same syndrome 25 years before.[1] They also cited three Chinese families with Graves' disease and de novo periodic paralysis.[2,3] The first two families were reported by McFadzean and Yeung[2] and the third family by myself.[3] The latter family is unique in that the affected members had "hashitoxicosis" (Graves' disease and Hashimoto's thyroiditis).

In a recent article, Sum and co-workers reported on two Chinese brothers with thyrotoxic periodic paralysis; two other brothers and a maternal uncle had thyrotoxicosis with no periodic paralysis.[4]

The occurrence of familial thyrotoxic periodic paralysis may be more common than is presently appreciated. It is hoped that further studies will add more insight into such an association.

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Seminars in Health Care Delivery

National Health Insurance in America—Can We Practice With It? Can We Continue to Practice Without It?

KEVIN GRUMBACH, MD, *San Francisco*

This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

Health insurance in the United States is failing patients and physicians alike. In this country 37 million uninsured face economic barriers to care, and the health of many suffers as a result. The "corporatization" of medical care threatens professional values with an unprecedented administrative and commercial intrusion into the daily practice of medicine. Competitive strategies have also failed their most ostensible goal—cost control. In contrast, Canada offers a model of a national health insurance plan that provides universal and comprehensive coverage, succeeds at restraining health care inflation, and does little to abrogate the clinical autonomy of physicians in private practice. I propose that American physicians relent in their historical opposition to national health insurance and participate in the development of a universal, public insurance plan responsive to the needs of both patients and physicians.

(Grumbach K: National health insurance in America—Can we practice with it? Can we continue to practice without it? West J Med 1989 Aug; 151:210-216)

The painting "The Doctor" by Sir Luke Fildes (Figure 1), rendered a century ago, conveys many attributes that the medical profession still values: compassion, patience, commitment to patients' welfare. The physician's expression in the painting is also troubled, and I have always imagined this is because the child has tuberculosis or some other endemic disease of that era that he is powerless to cure.

In 1950 reproductions of this painting appeared in thousands of physicians' offices throughout the United States. Congress was debating President Truman's national health insurance proposal, and the painting was a cornerstone of a multimillion dollar campaign by the American Medical Association against a universal government insurance plan. Below copies of "The Doctor," the following text was printed:

Keep Politics Out of This Picture

When the life—or health—of a loved one is at stake, hope lies in the devoted service of your Doctor. Would you change this picture? Compulsory health insurance is political medicine. It would bring a third party—a politician—between you and your Doctor. It would bind up your family's health in red tape. It would result in heavy payroll taxes—and inferior medical care for you and your family. Don't let that happen here![1(p47)]

Truman's plan was but one in a succession of national health insurance bills that have gone down to defeat in the United States, largely due to the opposition of the physician lobby.

But if we were to transport Sir Luke Fildes's doctor to the bedside of an ill child in the United States in 1989, I wonder what would be causing him to continue to have such a worried expression? Rather than despair about untreatable tuberculosis, perhaps these concerns would be foremost on his mind now:

How am I going to be able to hospitalize this child to treat her asthma, when her family doesn't have any health insurance?

or

Why did I let the utilization review officer for the family's IPA [independent providers association] plan pressure me to discharge this girl before her cellulitis was sufficiently improved?

or

Who's going to help me care for this Medicaid patient with leukemia, now that the only pediatric oncologist in the county no longer accepts Medicaid referrals?

A text to accompany "The Doctor" expressing the dilemma facing physicians and patients today might better read

Keep Business Out of This Picture

When the life—or health—of a loved one is at stake, you should have access to the services of a doctor. Would you change this picture? Transforming medicine into a commercial commodity rather than a professional service is bad medicine. It brings a third party—health plan bureaucrats—between you and your doctor. It binds up your family's health in red tape. It is resulting in wasteful health care expenses and inaccessible medical care for 50 million uninsured and underinsured Americans. Don't let this continue to happen here!

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ABBREVIATIONS USED IN TEXT

DRGs = diagnosis-related groups
GNP = gross national product
HMO = health maintenance organization

Rapid transformations are occurring in the financing and reimbursement of health care in the United States.[2] Physicians, who have tenaciously defended their professional interests against the perceived threat of government domination, now confront a market-driven health care economy in which private, corporate forces are eroding physicians' autonomy and influence. For consumers, health care is becoming exceedingly costly and inequitable. In contrast, national health insurance in Canada has dealt more successfully with preserving professional values while promoting universal access and reasonable cost control.

As the quality of our health insurance system deteriorates to the detriment of physician and patient alike, I propose that physicians relinquish the antiquated notion of national health insurance as the most dreaded of contagions and reconsider the merits of a universal public insurance plan.

The Uninsured

Health insurance in America is a lot like a hospital gown. At first glance it appears to give patients adequate coverage, but when looked at from another angle, embarrassing segments of the population remain exposed. The problem of uninsurance—affecting 37 million Americans—is one of the most glaring flaws in our health care system.[3] In California 5.2 million residents—or 22% of the population younger than 65—are uninsured. This proportion has risen from 17% eight years ago.[4]

The uninsured are not simply marginal elements of society. Nearly 70% of the uninsured have incomes above the poverty line, and most uninsured adults are employed. Full-time, full-year employees constitute the largest single category of uninsured Californians. A quarter of the uninsured are children, many of them dependents of working parents.[5]

Even for those employed in health care fields, health insurance benefits can be a fragile commodity. Last year in San Francisco, licensed vocational nurses and other hospital service workers went on strike when threatened with a dramatic reduction in employer contribution to health insurance for dependents. In my own practice at San Francisco General Hospital, I see a young uninsured girl with asthma whose mother is an eligibility worker at our hospital but cannot afford the $100-a-month premium to add her daughter to her insurance plan.

Figure 1.—The photograph shows the painting, "The Doctor," by Sir Luke Fildes (1844-1927), Tate Gallery, London.

TABLE 1.—*Indicators of Access to Medical Care by Insurance Status*

Indicator	*Insured*	*Uninsured*
Physician visits per year among people in fair or poor health, average No.*	10	6
People with no regular source of medical care, %*	16	31
Children younger than 6 years with up-to-date immunizations, %†	94	81
People with serious symptoms‡ who saw a physician within 30 days, %†	61	32

*From the Robert Wood Johnson Foundation.[10]
†From Freeman.[11]
‡Serious symptoms are bleeding other than nosebleeds or menstrual periods, dyspnea after light exercise, syncope, exertional chest pain, or unintentional weight loss of greater than 4.5 kg (10 lb).

At the same time that working families are losing health insurance coverage, public insurance programs for the poor also are becoming increasingly threadbare. The proportion of low-income Americans receiving Medicaid fell from 63% in 1975 to 46% in 1985.[6] The ebbing of the Medicaid "mainstreaming" ideal was accentuated in California when the state eliminated the "medically indigent adult" category in the Medi-Cal program (the state's Medicaid) in 1982, terminating public insurance for 270,000 Californians.

Consequences of Uninsurance

Health insurance is indispensable in the expensive context of health care today, both to protect against the financial calamity of catastrophic illness or injury and to promote access to basic medical care. While cases of patient "dumping" have been the most dramatic examples of patients suffering from a lack of insurance and have captured the most headlines (P. Aleshire, "East Bay Hospital 'Dumping' Tragedies Lead at Last to Legislative Reform," *Oakland Tribune,* October 4, 1987, p B-1),[7,8] studies have documented a more pervasive trend of impaired access to health care for the uninsured (Table 1).[9-11]

This diminished access, in turn, contributes to preventable morbidity and mortality. In a prospective study, a measurable deterioration in health—including preventable deaths—was found to follow the loss of health insurance in a cohort of former Medi-Cal patients.[12,13] The historical declines in the incidences of measles, mumps, and pertussis in the United States have all taken unprecedented upswings in the mid-1980s, at a time when many uninsured children are facing barriers to immunization.[14,15] Cutbacks in Medicaid and other public health services have also been related to the sudden rise in infant mortality that occurred in Boston in the early 1980s[16]; the stagnating overall national infant mortality rate has dropped the United States to 19th place in the world.[17]

Physicians, too, are caught in the dilemma of the uninsured. Even though many private physicians offer sliding scale fees or similar arrangements to their uninsured patients,[18,19] a major illness—and its attendant need for costly hospital care—can subvert these efforts to maintain continuity of care in the private sector.

The case of a patient I admitted to San Francisco General Hospital typifies this predicament. As a working uninsured

person, she received her initial evaluation for shortness of breath at her usual private physician's office. When a chest x-ray film revealed a large pleural effusion requiring inpatient evaluation and treatment, both the patient and her physician decided that admission to the county hospital, rather than a private facility, would be in the patient's financial interest, although it required the private physician to withdraw from formal management of the patient's hospital care. After admission, her condition rapidly deteriorated, leading to death from complications of lung cancer. Uninsurance severed a long-standing patient-physician relationship at a time when continuity of care was most needed.

The Coming of the Corporation

Uninsurance would be a liability in any era, but a number of converging trends in the 1980s are rendering the uninsured particularly vulnerable and underscore the more odious aspects of the transformation occurring in our health care system. Paul Starr, in his book *The Social Transformation of American Medicine,* dubbed this phenomenon "the coming of the corporation."[2] Other commentators have expanded the vocabulary of transformation with descriptions such as "industrialization," "privatization," "monetarization," "destabilization," and even "mega-corporatization."[20-24] All are attempts to capture the flavor of a system featuring more prominent roles for investor-owned, for-profit enterprises, health maintenance organizations (HMOs) and other managed care plans, and competitive market strategies to guide the distribution and financing of care.

There is good cause for physicians and patients to feel apprehensive about the corporatizing of health care. David Kinzer, former president of the Massachusetts Hospital Association, recently wrote in *The New England Journal of Medicine,*

> [I]ntensifying competition will move the country into a kind of regulatory twilight zone in which there will be impossible intrusions on the social mission of hospitals and on the professional prerogatives of attending physicians. One signal of this is what some privately controlled HMOs are already doing to dictate the practice styles of their participating physicians—all in the name of making money. Some of these intrusions are things that until recently *no government regulator would have dared,* such as refusing to pay for any presurgical days in the hospital . . . or dictating to which doctors a physician is permitted to send referrals *[accents added].*[25]

In addition to "dictating practice styles," certain HMOs and independent provider associations are introducing commercial incentives to physicians that challenge the very principle of professionalism in medicine. Most notorious are capitated arrangements that put primary care physicians at direct financial risk for using patient care resources, either by deducting the costs of laboratory tests, x-ray films, and specialty consultations from the capitation payment or by selectively distributing "withheld" portions of fees to reward physicians for cost-minimizing behavior.

To be sure, fiscal considerations in the practice of medicine are nothing new. Fee-for-service reimbursement has its own financial incentives to overtreat patients. And physicians have always been coy about acknowledging the entrepreneurial side of medicine. (The health economist, Uwe Reinhardt, once retorted to Arnold Relman that he would rather deal with a businessman who calls himself a businessman and drives a Lincoln than with a businessman who professes to be a saint and drives a Cadillac.[26]) But the development of putting physicians so directly at risk is a different magnitude of

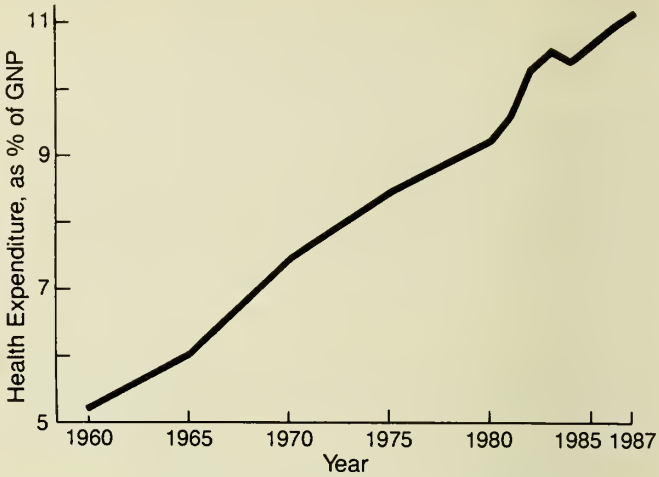

Figure 2.—The US health expenditures, as a percent of the gross national product (GNP), are shown (from Arnett et al[30] and *San Francisco Chronicle,* Nov 19, 1988, p 2).

commercialism that more acutely threatens physicians' moral obligation to act in the best interest of their patients.[27,28]

Relman, editor of *The New England Journal of Medicine,* has cautioned about the threat to professional values as physicians are submerged in a more explicitly commercial and corporate-dominated medical marketplace:

> A physician cannot easily serve his patients as trusted counselor and agent when he has economic ties to profit-seeking businesses that regard those patients as customers. . . . Conflicts between the altruistic ideals of medicine and the financial imperatives of business will almost certainly be resolved in favor of the latter by corporate managers whose jobs and financial advancement are at stake.[29]

The Failure of Cost Control

In all fairness, none of the ardent proponents of the corporate transformation of medicine have claimed that a more egalitarian, accessible, and provider-friendly system was a goal of this transformation. Cost control has been the driving force behind the policies of our era. Perhaps there would be some consolation for all the destructive aspects of these changes if we had at least attained meaningful cost control, but such has certainly not been the case. Health expenditures, expressed in Figure 2 as a percent of the gross national product, have escalated as much as ever during the past decade ("Health Costs Show Biggest Rise in 4 Years," *San Francisco Chronicle,* November 19, 1988, p 2).[30]

The unabated inflation in health care spending may seem surprising in view of a number of trends that should be promoting savings, such as the reduction in hospital admissions and length of stays. These reductions have been offset, however, by large increases in spending in other dimensions.[31]

One of the largest inflationary components of the health budget has been administration and marketing. Between 1975 and 1985, the costs of administering health insurance rose 655%, twice the rate of the rise of spending for physician and hospital services and three times that for medical research.[32] Dizzying amounts of billing, utilization review, and related administrative tasks have been a boon to health sector employment, except that most of the new employees are white collar rather than white jacket. The number of administrative personnel in health care fields is rising three times faster than the rate of increase of physician manpower.[33] In addition, while the exact amounts expended on adver-

tising are uncertain, it is becoming increasingly difficult to evade health plan hype pitched over the airways, on television, and across billboards.

Moreover, competition has not bred the leaner, more efficient system envisioned by free-market afficionados. Instead, it has promoted a great deal of cost shifting posturing as cost control.[23,31,34-36] For example, competitive hospital contracting has eliminated the extra insurance revenues private hospitals formerly used to cross-subsidize charity care to the poor and uninsured. As a result, private hospitals—particularly for-profit ones—have become much more selective about screening out uninsured patients and diverting them to county hospitals and clinics.[7,21,37] "Savings" to private hospitals and insurance plans are merely then shifted to the public sector, where the costs eventually turn up in the local tax bill.

A related phenomenon has occurred with HMOs. Although HMOs economize in their own inpatient expenditures,[38,39] the introduction of HMOs into a market area does not result in any savings in the overall cost of hospital care in the area. Rather, it appears that non-HMO institutions' costs go up commensurate with the decrease in HMO expenditures.[40]

Diagnosis-related groups (DRGs) also illustrate the elusiveness of cost control. Inpatient costs for Medicare may have been restrained, but the fallout from DRGs has been more intensive, extensive, and expensive care in the ambulatory sector and the discharge of sicker patients to nursing homes.[41,42] Both outpatient and long-term care services require greater out-of-pocket payment by Medicare recipients.

Cost shifting has taken on the properties of a force of nature, obeying its own version of Newton's Third Law of Physics: For every force, there is an equal and opposite force. When one segment of the health care budget is pushed, it bulges out in another area. Attempts to contain costs in one area, such as DRGs, elicit inflation in another, such as nursing home costs. In our disorganized health care system where no single plan has control over and responsibility for the entire operation, Newton's law of cost shifting undermines meaningful health care planning. Multiple private and public plans each push away at their corner of the system, deforming the structure but ultimately not containing it.

Principles of National Health Insurance

Given that current health care policies are failing patients and physicians on so many scores, could we expect better from national health insurance?

National health insurance should be built on a few fundamental principles.[43] The most basic is that of universality—that is, the plan should provide coverage for everyone, rather than be categoric for selected groups on the basis of age, income, level of illness, or other such divisive criteria. The failings of the Medicaid program reveal many of the problems with a nonuniversal government insurance plan. By limiting its beneficiaries to poor women and children, the most politically disempowered population, and the disabled and elderly poor, the most costly of patients to care for, Medicaid has assumed an unsupportable quotient of political and actuarial liability. Medicare, categorical by age but more universal by dint of its lack of income criteria, is a much more viable program.

The plan also should be comprehensive, covering all medically necessary services. Medicare and Medicaid also provide a lesson in the foibles of inadequate comprehensiveness. A health insurance plan for the elderly that does not cover long-term care operates about as well as a surgeon without a scrub nurse. By excluding nursing home reimbursement, Medicare has not saved the overall system money but merely shifted these unavoidable expenses onto patients and Medicaid.

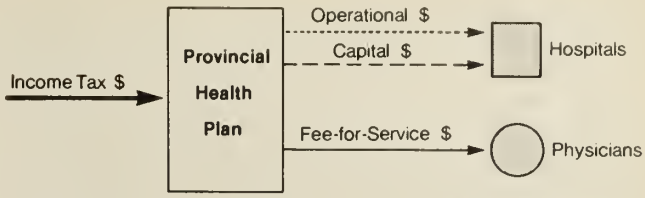

Figure 3.—The schema shows the financing and reimbursement structure of national health insurance in Canada.

National health insurance also should be progressively financed to spread health care costs fairly. It should be efficient, providing the best value for our investment through reasonable cost control. Finally, it should preserve clinical independence for physicians.

Mentioning national health insurance to physicians typically elicits a downpour of skepticism. The gentler commentary tends to be that these ideals are all well and good but are too utopian and impractical. The stormier discourse tends to focus on the following criticisms:

- It would cost too much to extend comprehensive insurance to everyone.
- It would impose a terrible government bureaucracy on health care and prevent physicians from practicing quality care.
- It would ration care.
- It would prevent physicians from earning a respectable income.

Probably the best way to evaluate the legitimacy of these criticisms is to examine a national health insurance program already in existence. A natural place for comparison is our northern neighbor, Canada, a nation with many cultural and economic similarities to the United States where physicians in private practice work within the structure of national health insurance.

National Health Insurance in Canada

The Canadian health insurance program (Figure 3) has existed in its current form since 1971.[44-47] It is administered at the provincial level. All residents are eligible for insurance. Funding derives from the general provincial and federal tax revenues; there is no specially designated medical tax as there is for Medicare in the United States. A few of the provinces supplement these revenues with small premiums. Revenues flow into a central provincial health plan, which then reimburses providers. Private health insurance has been eliminated, except for covering some minor amenities such as private rooms. The benefits of the plan are relatively comprehensive, covering all physician and hospital services. Long-term care has recently become a stronger element as well.[48] Dental services and outpatient medications are not covered, although provinces usually subsidize these costs for the poor.

In terms of reimbursement, physician payment is on a fee-for-service basis. Physician billing consists of a state-

ment submitted to the government on a monthly basis. The provincial medical associations negotiate with the health plan for annual fee adjustments, and the associations exert considerable influence over how fees are distributed among specialties.[46,49] Canada recently banned extra billing, a practice where some physicians billed patients directly for fees in excess of the government fee schedule. The current situation is thus analogous to mandatory Medicare assignment.

In reimbursing hospitals, Canada has separate processes for funding operational and capital expenditures.[44,45,50] Operational costs refer to the costs associated with running a hospital—paying nurses, laboratory technicians, and ancillary personnel, purchasing medications and supplies, cooking meals. The plans reimburse these costs through a global annual budget. Every year each hospital must submit a budget to the plan, anticipating the volume and acuity of care, and after some haggling over this budget, the government proceeds to fund the hospital in regular installments over the year. There are consequently no itemized bills for each antibiotic or surgical procedure or hospital day, nor are there DRGs to submit or authorizations for stay to solicit.

Funding for capital expenses—the costs of building a new intensive care unit or purchasing new technology—occurs through a different mechanism. For these funds, a hospital must apply to the health plan for a special grant that is kept separate from the operational budget. To approve the grant, the government must determine that community needs justify the investment in new technology or expansion of services.

That, in brief, is an overview of the mechanics of Canadian national health insurance. How successful has this program been?

First, in terms of equitability, Canada clearly has succeeded in achieving near-universal coverage: 95% of the population is insured, and Canada is not plagued by the problem of uninsured persons that pervades the United States.[46,47]

Has this universal coverage spelled financial ruin for Canada, as the Cassandras predict for national health insurance in the United States? To the contrary, health care costs are much lower in Canada than in the United States. In 1987

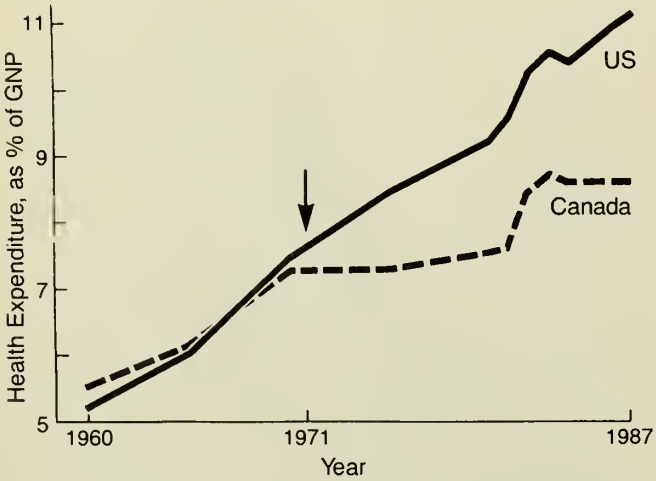

Figure 4.—National health expenditures are shown for the United States and Canada. In 1971 **(arrow)** Canada fully implemented its national health insurance (from Arnett et al,[30] Barer et al,[49] Schieber and Poullier,[51] and *San Francisco Chronicle* [Nov 19, 1988, p 2]). GNP = gross national product

TABLE 2.—*Administrative Costs for Health Care in the United States and in Canada**

Administrative Cost	*United States*	*Canada*
Costs of administering health insurance (overhead and profits), as a percent of total insurance costs, %	12.0† 2.7‡	2.5
Physician overhead, as a percent of gross earnings, %	45.0	36.0
Hospital administration, as a percent of total hospital expenses, %	18.0	8.0

*From Waldo et al[32] and Himmelstein and Woolhandler.[54]
†Private insurance plans in the US.
‡Federally administered insurance plans.

Canada spent 8.6% of its GNP on health care and the United States spent 11.1%.[29,46,49,51] As Figure 4 shows, costs in the two countries were on overlapping curves until 1971, the year Canada fully implemented comprehensive national health insurance.

Because Canada and the many other nations with national health insurance have achieved much greater success at tempering health care inflation than has the United States, many observers now conclude that a national health plan is a necessary element of controlling health care costs, rather than a stimulus for accelerated spending.[44,45,52,53] A single payer for health care that can prospectively set the broad boundaries of spending appears to be much more effective than free-market competitive strategies at quieting the Newtonian forces of cost shifting.

Has economy of health care in Canada come at the sacrifice of quality, however? One way that national health insurance has saved Canadians money without detracting from clinical care is by reducing administrative waste. One study of administrative expenses estimated that a Canadian style system could save the United States 8% of its overall health costs—roughly $30 billion in 1983.[54] As Table 2 shows, global budgeting and simplified physician billing contribute to a more efficient system.

In regards to the savings accrued from differences in actual clinical practice, it does appear that the Canadians practice a less "intensive" style of medicine and are less enraptured by technology.[55] Fewer surgical procedures are done on a per capita basis in Canada than in this country.[56,57] Hospital budgeting policies have placed more limits on the diffusion of expensive new technology. For example, Toronto has only one radiation therapy unit and Boston, a city of comparable population, has six.[46] A survey from the early 1980s revealed that the province of Ontario had 1 computed tomographic scanner for every 250,000 residents but the US ratio was 1 per 150,000 people.[58]

Whether this is rationing or simply rational is difficult to say. In view of several recent reports of considerable inappropriate use in this country of procedures such as endarterectomy, coronary angiography, endoscopy, and pacemaker placement,[59,60] one could argue that "less is more" for the health of Canadians. On the other hand, patients do experience some delays in obtaining elective but necessary procedures. Unlike our hospitals awash in vacant beds, Canadian hospitals are sometimes overcrowded, and during busy seasons patients may be held in emergency departments waiting for beds to become available.[61]

If this constitutes rationing, it is difficult to detect any

major adverse outcomes on health. Health indicators, such as infant mortality and life expectancy, are as good or better in Canada than in the United States.[58] Nor does it seem to bother the Canadians, who continue to rate their health insurance system very favorably in polls.[46] Whatever else may be said about rationing in Canada, it applies to all Canadians. Our northern neighbors do not have to explain what moral code justifies refusing organ transplantation to the poor but not to the well-to-do, something we agonize over when a state like Oregon eliminates transplantation from its Medicaid services.[35,62]

What is the Canadian physician's point of view? While there has been some restraint in the growth of physician incomes under national health insurance, physicians continue to be the most affluent professionals in Canada, earning nearly five times the average Canadian's income and maintaining a preeminence over lawyers, accountants, and engineers.[44] The average net income for general practitioners in 1986 in Ontario province was $81,000 (in US dollars).[46] Private, office-based family practitioners in the United States had a median income of $86,000 the same year.[63] While the provincial health plans do not release more detailed income data by specialty, the Canadian relative value scale tilts less generously towards the procedural specialties than do traditional fee scales in the US, resulting in a narrower skew of income between primary care physicians and specialists.

If Canadian physicians have sacrificed some small degree of earning power under national health insurance, they have reaped a number of benefits. The government subsidizes all medical schools, and physicians consequently do not enter practice tens of thousands of dollars in debt.[48]

For practitioners, I have described the simple billing procedure under national health insurance. Imagine having to fill out the same billing form for an entire month's worth of visits and being able to expect prompt reimbursement within four to six weeks from a single payer! Imagine not having to send unpleasant collection notices to patients. And imagine the relief of being able to treat any patient who walks into your office, without first asking whether he or she has insurance and, if so, are you a participating provider in that plan.

In addition to simplified billing, physicians face much less bureaucratic meddling in their practices in Canada. Canada contains costs through the closed structure of a single-payer system, not by policing the day-to-day clinical decisions of physicians. Unlike current insurance trends in the US, the Canadian system has done little to abrogate the clinical authority and judgment of physicians in matters of direct patient care.[44,64]

In summary, the Canadian national health insurance program has proved reasonably successful at balancing its social, fiscal, and quality-of-care obligations. The system does impose some limits, but these limits are applied universally in contrast to the de facto rationing of care on the basis of wealth that occurs in the United States. It preserves physicians' autonomy and professional integrity. It makes it all too apparent that with the extra 2.5% of our GNP that we spend on health care above what the Canadians spend, we should be able to provide a high quality of care to all Americans without a major insult to physician income or technologic progress.

Robert Evans, a health economist from Vancouver, has remarked that there are only two things that Canada does better than the United States: play hockey and organize medical care. Now that our country has imported Wayne Gretzky, perhaps a national health insurance plan will follow.

What Lies Ahead

By continuing on our current health care trajectory in the United States, we are likely to arrive at an increasingly multi-tiered system providing a minimal and explicitly rationed level of care to the poor, a fiercely competitive, HMO-dominated tier of care for the middle class, and a "luxury line" style of care for the affluent. While Thurow admonishes against proceeding in this direction,[65] Kitzhaber advises accepting its "inevitability" and seems to prefer such a system to national health insurance.[35] With the exception of affluent consumers and physicians specializing in diseases of the rich, few will be satisfied receiving or providing care in this type of rapaciously inequitable, "corporatized" system.

Undoubtedly there will be no shortage of proposals to solve this deepening crisis. Most strategies will attempt to patch some of the more glaring gaps in coverage with modest reforms without challenging the structural premises of the health insurance system. For example, mandated employer-sponsored insurance has the allure of political expediency with a minimal disruption of existing insurance mechanisms. Employer mandates have been adopted in Hawaii and more recently in Massachusetts, and several California legislators—most notably Assembly Speaker Willie Brown—are drafting comparable measures. Although billed in Massachusetts as providing universal coverage, the Massachusetts example suggests that reforms such as employer mandates will in fact still leave many persons without insurance, perpetuate a fragmented insurance structure in which rampant cost shifting undermines real cost control, and further sacrifice professional values and autonomy to the commercial interests of competing health care enterprises.

Enthoven and Kronick have recently proposed a more ambitious plan that attempts to provide universal coverage through a complex mix of private and public payers.[66] These payers would act as brokers (called "sponsors") to purchase group coverage from a variety of private, competing managed care plans. Cost control would hinge on the principles of corporatization: the plan emphasizes competition between plans and prudent purchasing of coverage by price-sensitive consumers. Under the plan, the authors predict the "decline" of traditional fee-for-service, individual and single-specialty group practices due to their economic inefficiency. This strategy has implications for the future context of medical practice that are decidedly different from a single-payer system, such as Canada's, that relies more on administrative efficiency and global budgetary planning.

Reinhardt, a native of Germany who immigrated to Canada before settling in the United States, recently speculated about what lies ahead for American providers:

> The nation's physicians and hospitals may yet come to appreciate that the free market so many of them dreamed of in the 1970s is actually a torturous instrument designed to visit on them daily uncertainty, step-by-step monitoring of their clinical decisions by external lay boards, and morally vexing tradeoffs between economic security and their professional code of ethics. From that vantage point, the less directly controlled, clinically more unfettered, and financially more secure setting in which, say, Canadian physicians and hospitals ply their trade under the neighbor's national health insurance system may gain respectability among American providers.[34]

Reinhardt's use of the word "respectability" is apt. The notion of national health insurance has historically not gotten

much respect from physicians in the United States. At least that is the common perception of physicians' attitudes. One poll from the 1970s, however, showed that slightly more than half the physicians surveyed actually favored national health insurance; three quarters thought that their colleagues opposed it.[67] A group of physicians, Physicians for a National Health Program, recently published a specific proposal for a health care system modeled on the Canadian plan.[68,69]

It is time for physicians favoring a national health insurance plan to come out of the closet and become advocates of a universal plan that can uphold our professional values. By continuing to fight national health insurance at all costs, physicians are abetting a transformation that threatens to destroy much that is honorable and satisfying about the practice of medicine.

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Commentary

Lessons From the Frozen North

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Although the issues of the cost of and access to health care in the United States have been a matter of debate for some time, the magnitude of the problem has increased the urgency and raised the question of possible alternatives to the present US health care system.[1-3] Much of the discussion has focused on the Canadian health care system, which delivers care to virtually the entire population at 8.6% of the gross national product (GNP) compared with 11.4% for the United States. Although recent articles have alluded to the economies of the Canadian health care system,[4-8] there has been relatively little written about how the system actually works.

Having just returned to the United States after 12 years of practicing academic internal medicine in Canada, I have had an opportunity to assess both the strengths and weaknesses of the Canadian system and what would be required to implement such a system in the United States. Let me preface my comments by stating that the Canadian health care system does work. In 1965 health care costs in the United States and Canada were identical at 6.1% of the GNP. In 1988 the cost in Canada was 8.6% of the GNP compared with 11.4% in the US. For this lesser amount, approximately 95% of the Canadian population received essentially total medical care.

The Canadian constitution assigns the primary responsibility for health to the ten provinces.[4] The federal government defined three major criteria to be satisfied if provinces were to receive federal support—which now amounts to about 38% of the cost of the health insurance plans.

- Accessibility: All medically required services were to be covered without dollar limit, deterrent fee, or extra billing.
- Portability: The benefits should be portable anywhere inside Canada or out—a Canadian who became ill and required treatment in the US would be reimbursed for emergency care at Canadian rates, for example.
- Nonprofitability: The plan must be administered publicly and on a nonprofit basis. The province could not use private insurance companies nor could it profit, although it could and does lose money.

This discussion will deal with the Ontario Health Insurance Plan (OHIP) because it is the one with which I am most familiar. The federal government provides about 38% of the money while individuals or businesses provide 25% through premiums; the Ontario government supplies the rest. Ontario is spending about 30% of the provincial budget on its health care system. The manner in which the money has been spent for health care has remained relatively constant, with about 60% of the budget spent on the hospital sector, 25% on physicians, and 10% on drugs. The remaining 5% is spent on miscellaneous items like physiotherapy. These fractions are about the same in the United States, with slightly more going for physician reimbursement. The major causes of escalation in health care costs in Ontario are rising hospital costs and an increasing volume of physician claims. As might be expected, this is of serious concern to the provincial government. The health budget represents a substantial portion of the total provincial budget. Perhaps of even more concern is the fact that the government has little direct control over this portion of the budget.

What do patients get in terms of health benefits?

- All necessary medical care, whether inpatient or outpatient;
- All necessary drugs, biologicals, and diagnostic tests, as well as a broad range of outpatient services;
- Physicians' services, which cover all medically required services rendered by medical practitioners in hospitals, clinics, or physicians' offices;
- Additional benefits such as drug coverage, chiropractic, and physiotherapy.

The preponderance of Canadian hospitals are nonprofit and owned and operated by voluntary agencies, municipalities, or institutions such as universities. Most of these hospitals operate under a global budgeting system in which a base budget was established in 1969 using previous years' costs, with an annual inflationary increase to this base added by the government. If the need can be justified, additional funding can be obtained. In fact, certain "life support systems" such as renal dialysis, coronary artery bypass, and cancer chemotherapy are funded outside the global budget. Operating expenses are separated from capital spending, and other arrangements such as private fund-raising must be found to finance hospital construction—but governmental permission is still required.

Physicians are reimbursed directly by the Ontario Health Insurance Plan. A physician fills out a form after seeing a patient, listing appropriate charges, and the plan reimburses the physician minus 10% for overhead. Administrative overhead for billing and collecting is substantially less than in the United States because there is a single payer who does not have to monitor or challenge the medical services delivered.[8] Formerly a physician in Ontario could "opt out" of the system and bill a patient directly for more than the authorized charge. The patient would be reimbursed for 80% of the

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authorized fees. This alternative no longer exists, however. Ontario physicians must practice either within the system or not at all: a physician cannot opt out completely and charge patients. The rationale for this prohibition is based on governmental concern that all the specialists in a small town—anesthesiologists, for example—might opt out, thus violating the criterion of accessibility.

The Ontario Medical Association negotiates the amount available for physician reimbursement with the Ontario Health Ministry every two years. These negotiations reflect inflationary forces, the volume and nature of work done by physicians over the previous period, and the current state of the provincial economy. Ontario physicians in the past have withdrawn services over the amount of money made available by the ministry. There is a great deal of unrest and resentment at present over the 1.75% increase recently granted by the Ontario government after contentious negotiations. The actual distribution of these funds is determined by the physicians themselves. In an interesting session appropriately called the "bear pit," members of the Ontario Medical Association, representing the various specialties, decide among themselves how much each procedure is worth. (Imagine a general internist, cardiologist, and surgeon deciding how much an endoscopy procedure is worth!) There are no governmental controls over the volume of patients seen by an individual physician. When Ontario ended extra billing in 1984, the volume of billing by physicians increased by 15%. There are also no professional standards review organizations or second opinions required for surgical procedures. In fact, no charge by a licensed physician is disallowed if it is within the purview of OHIP.

In 1986 total health care expenditures were $1,726 per capita in the US and $1,256 in Canada. How are costs actually controlled in the Canadian health care system? In the 1960s the Ontario Health Ministry rationalized tertiary cardiac care by limiting cardiac catheterization and open heart operations to a selected number of university teaching hospitals. In Toronto, with a population of 2.5 million and a wide referral base, there are 13 hospitals, and 3 provide cardiac surgery. With a similar population but a much narrower referral base, San Diego has 36 hospitals, and cardiac surgery is done in 9 of these.

There have been several studies examining cost containment in the Canadian health care system.[5-7] In Canada hospital costs rose 86% related to inflation from 1968 through 1981, compared with 130% in the United States. Real inputs, which are an economic measure of cost in terms of the factors employed to produce a goal or service, increased in Ontario during this same period by only 16% compared with 101% in the US.[6] In the hospital sector these factors include both labor—nurses, administrators, and aides—and nonlabor units—buildings, equipment, and supplies. Increases in inputs are equivalent to increases in the quality of care by employees and to increases in supplies and equipment. This increase in inputs in the US health care system suggests that patients are getting more rather than simply having the same care become more expensive. Feldstein and Taylor attributed these increases to the growth in health insurance, with only a small proportion of total hospital costs borne directly by patients at the time hospital services are used.[9] This separation of patients from hospital costs is accompanied also by the separation of physicians from hospital costs. Physicians are responsible for allocating most of the hospital resources, yet they bear none of the costs associated with these allocations.

What have been the consequences of the fewer inputs on the quality of hospital care in Ontario? Detsky and colleagues concluded that there was no major effect.[7] The distribution of health care in Ontario had not changed, and academic teaching hospitals had not gained at the expense of suburban and rural hospitals. Similar trends were observed in the growth of hospital costs and real inputs in both teaching and nonteaching hospitals. The teaching hospitals started with a larger base, reflecting their academic tertiary care role.

Britain, with the long waiting times occurring in its National Health System, has overcontrolled health care. Although there are concerns, Canada has not yet severely rationed health care. The Canadian health care system provides excellent care to all residents on a fully prepaid basis with no upper dollar limits. Canadians live as long as do people in the United States and enjoy a similar health status—in fact, better, if perinatal mortality is considered. So far, this has been achieved at a cost the country has been able and willing to afford. Canada has not yet rationed care, but governmental controls are in place that would allow rationing of health care to occur, which has made Canadian physicians very anxious. Ontario physicians basically distrust governmental intentions, and this attitude makes negotiations between the two groups difficult. The distrust has been heightened by current provincial government efforts to control the problem of patient volume by some form of capitation payment rather than fee-for-service. Despite the concern, it is clear that to control health care costs, there will have to be some way to put the provider—physicians, for example—at risk, whether by capitation or, preferably, by incentives. As long as the volume of patients can be determined by physicians, there is no real motivation for physicians to contain costs.

Although free access to health care is the cornerstone of the Canadian health care system, the process would function better with a minimal deterrent fee. If there are physician abuses, there are also patient abuses. Family physicians are the gatekeepers of the Canadian health care system. If a consultant sees a patient on a primary care basis, he or she will be reimbursed as a general practitioner. Virtually all patients, therefore, are referred to specialists by family physicians. Patients can always find family physicians who will refer them repeatedly to various specialists. Another defect in the present Canadian system is the lack of recognition of physician quality. All physicians are not equal, but all are reimbursed at the same rate regardless of training or length of time in practice.

Could the Canadian system of health care work here in the United States? There is no clear reason why it could not. Whether such a system would ever be implemented in the United States is another question entirely. A key aspect in the initial implementation of the Canadian health care system was cooperation among government, physicians, and insurance companies. Enthoven and Kronick have listed certain requirements that must be fulfilled for a politically viable health care proposal that would not fit with a Canadian type of health care system.[1] The National Leadership Commission on Health Care has addressed the three major problems of cost, quality, and access to health care. They have come forth with a set of recommendations that differ from but are not inconsistent with the Canadian type of system.

What is the proper role for academic medicine in addressing the current health care crisis in the United States? We cannot solve the problem by simply opening our hospitals as this is, at best, a temporary solution. Besides, that is not our mandate. We can, however, take an active role in educating the public about the dimensions of the crisis and possible solutions.

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Information

Clove Cigarettes

The Basis for Concern Regarding Health Effects

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UDAYA B. S. PRAKASH, MD, *Rochester, Minnesota*

The smoking of clove cigarettes has been associated with 13 cases of serious illness in the United States, including hemorrhagic pulmonary edema, pneumonia, bronchitis, and hemoptysis. We describe a patient in whom, after she smoked a clove cigarette, pneumonia complicated by lung abscess developed. Her lung disease may have been caused by aspiration pneumonia as a consequence of pharyngolaryngeal anesthesia from clove cigarette smoke. Clove cigarettes appeal to adolescents experimenting with smoking practices and may influence the development of later smoking habits.

(Guidotti TL, Laing L, Prakash UBS: Clove cigarettes—The basis for concern regarding health effects. West J Med 1989 Aug; 151:220-228)

A newly popular smoking habit has been developing in the United States.[1,2] Centered in California, this trend involves an exotic tobacco product called clove cigarettes, or "kreteks," a type of cigarette imported from Indonesia containing mixed tobacco and chopped cloves. The use of clove cigarettes achieved the dimensions of a fad in 1985, when imports peaked, but fell off rapidly afterwards due to extensive publicity reflecting concern over their health effects. Since then consumption has remained active at a reduced level amid signs that the major importers and distributors are prepared to make a major push if clove cigarettes were to be vindicated of health concerns. Although the active ingredient of clove, eugenol (4-allyl-2-methoxyphenol), and the popular spice itself have been used extensively in the practices of dentistry and the culinary arts, respectively, adverse health effects have not been reported. With the development of the habit of smoking clove cigarettes, however, several cases of pulmonary diseases associated with this fad have been described. Experimental studies involving animals have not shown pathologic processes akin to clinical findings in humans. The study of clove cigarettes and their implications for health also illuminates the factors that condition adolescent smoking habits, as well as the toxicology of a class of compounds previously of concern only as food additives and spices.

Availability and Consumption

Nearly all clove cigarettes imported into North America are manufactured by several large companies in Indonesia, where they have been widely used for a century. A small number are manufactured in the United States. In the 1970s, they became popular among young people in Australia and, in about 1980, among teenagers and young adults in southern California. Their earlier popularity among surfers suggests that this might have been the connection that introduced them into this country. Their popularity in Australia has since waned. Imports into the United States rose from 16 million in 1980 to 150 million in 1984, but fell following adverse publicity in 1985[1,2] and have declined further since (Figure 1).

Popular brands of clove cigarettes include Jakarta, Djarum, Gudang Garam, Krakatoa, Sampoerna "A," and many others, most with Indonesian names. They have been sold in colorful boxes of ten for about $2.50 in convenience stores, tobacco shops, "head shops," and sometimes drugstores (Figure 2) and are known as "cloves," "kreteks," or "chicartas" by users. Resale among young persons, particularly those younger than the legal age for purchasing tobacco products, is thought to have been a brisk trade in communities where they were popular. In mid-1984, an estimated 70,000 to 80,000 persons smoked them regularly. By 1987, this had fallen to around 25,000 smokers nationwide, of whom about 8,000 were in California. (These figures have been confirmed by the Specialty Tobacco Council, an advocacy organization for the industry.) Many more young people have smoked them on a casual basis. A particular appeal of clove cigarettes has been their identification with a youth-oriented life-style, particularly surfing and "new wave" music, as well as their exotic packaging. Although their sale to minors is forbidden by law, the fad appears to have been widespread among teenagers of high-school age and younger.[1-3] The extent of this fad among youth surprised many adults who were unaware of it until coverage in the news media in 1984 and 1985 gave it visibility.

We collected data on the extent of usage and trends in the penetration of this fad among young people in San Diego in 1982.[4] Our survey of 23 tobacco stores in San Diego indicated that 15 sold clove cigarettes; most of those that did not were small newsstands. Most specialty tobacco stores in the area reported that clove cigarettes were then among their most profitable products. By 1984, convenience stores in

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southern California also carried clove cigarettes, and anecdotal reports suggested that such operations were the major source for teenagers, including minors. Convenience stores now, according to industry sources, have discontinued sales for the most part, and by late 1987 only 5% were estimated to handle the product.

Aside from marketing surveys that are not circulated outside the industry, the most precise estimate of clove cigarette consumption for a defined population is that derived by Robinson and co-workers in an extensive survey of substance use among adolescents aged about 16 years in northern California under conditions of anonymity and isolation from school authorities.[3] Their data are summarized in Table 1. In this study of almost 1,300 predominantly white tenth graders, 20% of the boys and 26% of the girls indicated that they had at least experimented with clove cigarettes, and about 1% of each smoked them on a daily or near-daily basis. Among adolescents who use one or more substances daily, about 12% smoked clove cigarettes. Anecdotal evidence suggests that the use of clove cigarettes among adolescents who use at least one substance daily is almost always in addition to another habit, most likely the consumption of tobacco cigarettes or alcohol. This study showed clearly that clove cigarette use is part of an overall pattern of substance abuse that includes tobacco in other forms, marijuana, and alcohol and that this substance use is related to self-destructive and health-related risk-taking behaviors and poor performance in school. These associations were complex in their interrelationships, and clove cigarettes were but one small piece of the larger picture.

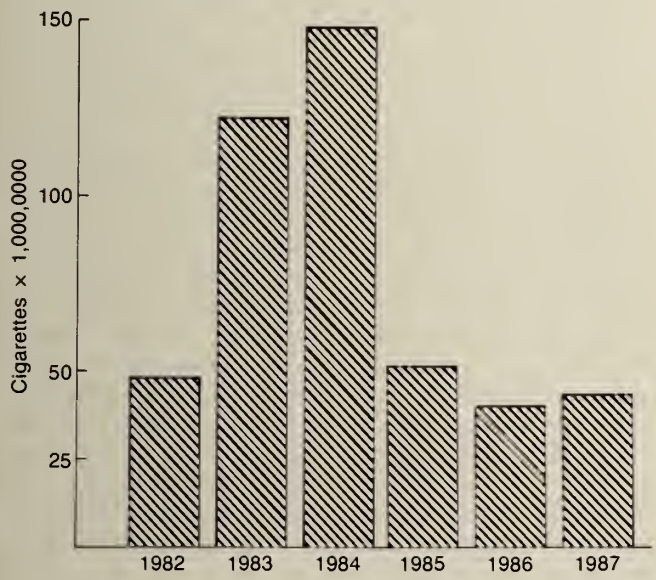

Figure 1.—The graphs show the imports of clove cigarettes into the United States from Indonesia since 1982 (from the US Department of Treasury, Bureau of Alcohol, Tobacco, and Firearms).

Figure 2.—Clove cigarettes are sold in small, brightly colored packages with exotic designs.

Composition and Toxicology

Clove cigarettes are made from tobacco compounded with about 30% to 40% minced cloves and have a pungently sweet odor and taste. The mode of smoking among younger smokers often resembles that used for marijuana cigarettes ("toking"). In this practice, a deep inspiration followed by a Valsalva maneuver maximizes delivery to the respiratory surface. How widespread this practice may be is not known, but anecdotal reports suggest that toking is fairly common among American users—possibly in mimicry of marijuana use—but not in Indonesia, where clove cigarettes are smoked in a conventional manner.

In considering the potential toxicity of clove cigarettes, it is useful to think of them as a product with all the known hazards of tobacco cigarettes, with the addition of unknown hazards associated with the chemical constituents of the clove.[5,6] Clove cigarettes deliver a higher tar content than most domestic American brands, although users usually do not smoke them as often as they would conventional cigarettes.[2] Tar deliveries range from 34 to 65 mg, nicotine from 1.9 to 2.6 mg, and carbon monoxide from 18 to 28 mg per cigarette. The high deliveries are probably due to a combination of four factors: the nature of the Indonesian tobacco used, the high weight of the cigarettes, the number of puffs required to consume them, and the tar residues left by the clove bud. Much of the smoke derived from a clove cigarette is a simple distillation of clove oil, without oxidation of the constituents. Indeed, the composition of distilled clove oil—as obtained by the combustion of a 100% clove cigarette—has been called "amazingly simple" and consists primarily of eugenol and related compounds (Figure 3).[7] Five compounds not previously reported in tobacco smoke at comparable levels have been identified in the particle phase of the clove cigarette smoke using gas chromatography and gas chromatography-mass spectrometry: eugenol, acetyl eugenol, β-caryophyllene, α-humulene, and caryophyllene ep-

TABLE 1.—*Clove Cigarette Use by 10th Graders in Northern California in 1985**

Characteristic	*Boys*	*Girls*	*All Subjects*
Respondents, No.	677	609	1,286
Use clove cigarettes, %			
Never	72	63	68
At least once	20	26	23
Frequency of current use, %			
At least monthly	7.4	9.9	8.6
Daily or almost daily	1.0	0.8	9.1
Frequency of current use (%) among those who used one or more substances daily†	NA	NA	12

NA=not available

*From Robinson et al.[3]

†71% smoked conventional cigarettes, 20% smoked marijuana, 7% drank alcohol, and 4% consumed chewing tobacco or drugs of various types.

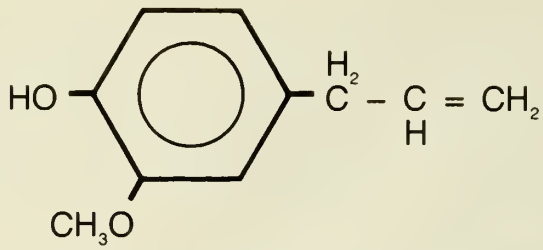

Figure 3.—The chemical structure of eugenol (4-allyl-2-methoxyphenol) and related compounds is shown.

oxide. All of these compounds have also been identified in natural clove oil.[2,7] These phenylpropene compounds are present at high concentrations in clove and nutmeg. Traces of eugenol are also found in conventional cigarettes. Conventional cigarettes painted with clove oil produce a similar smoke, with a somewhat lower delivery of eugenol and related compounds.[7]

Eugenol has a variety of pharmacologic and toxicologic effects (Table 2).[2,8-16] Clove oil is used extensively and safely as a topical dental anesthetic. This anesthetic activity may also cause numbing of the pharynx when clove cigarettes are smoked. Eugenol and its derivatives are being investigated for their effects on the central nervous system, especially as anticonvulsants. The neurotoxic effects of eugenol are particularly interesting because clove cigarette smoke is thought by many users to have a mild psychotropic effect.[17-19] Adolescent users often report that smoking clove cigarettes confers mild euphoria. It is reasonable to suggest that the relatively high concentration of eugenol likely absorbed by the inhalation route may be a euphoriant. The high nicotine level delivered may also contribute to the euphoric effect.

Before the clove cigarette issue emerged, toxicity testing of eugenol was limited to ingestion or topical application. Only one study assessed pulmonary injury. In this study, the intravenous administration of a dose of 0.1 ml per kg body weight was reportedly associated with the development of pulmonary edema and death in dogs, but detailed data and pathologic descriptions were not available.[20]

More recently two series of studies have become available.[6] In a preliminary study, LaVoie and associates at the American Health Foundation of Valhalla, New York, report that the intratracheal instillation of eugenol at levels not far above those achievable by smoking clove cigarettes resulted in massive acute hemorrhagic pulmonary edema.[21] Studies of the direct inhalation of clove cigarette smoke conducted by the Huntingdon Research Centre in Britain concluded that exposure to clove cigarette smoke in rats was associated with no greater detectable lung injury at 24 hours and at 14 days than exposure to commercial American cigarettes, however.[22-25] This study reported a lower delivery of carbon monoxide than that suggested by other analyses,[22,23] such as those done at the Oak Ridge (Tennessee) National Laboratory.[26] No study has addressed long-term effects.

All studies done to date on the toxicity of kretek smoke and its components suffer from problems of design and interpretation. A general problem is a doubtful statistical reliability due to the small numbers of animals tested. The statistical power of a study with only five animals per group, as in some of the Huntingdon studies, is low indeed. None of the studies replicate the pattern of kretek use by smokers and cannot address the problem in a way that is convincingly relevant to the clinical cases provided to date and to reports by kretek users. The pattern of kretek smoking cannot be easily duplicated in animal studies without controlling the airway and forcing oral delivery of the smoke in a variety of smoking patterns. In this regard, the inhalation studies are as unphysiologic as the intratracheal instillation experiments despite the known drawbacks of the latter technique. Another reason for uncertainty in applying data from studies of animals to the human situation is that there is considerable variation in toxicity among different species, such as the difference in the oral median lethal dose (LD_{50}) between mice and dogs—3,000 and 500 mg per kg body weight, respectively. Extreme caution must, therefore, be used in extrapolating the findings to humans.[6] A more fundamental issue is involved, however. Even convincingly normal findings in animals in a study with adequate statistical power—an ideal not achieved by the Huntingdon reports—cannot refute the evidence of human health effects based on clinical case reports. Studies of animals, by themselves, cannot refute clinical information. Inconsistent results in an emerging and complex area of toxicology are by no means the equivalent of negative results. A coherent picture of the toxicity of clove cigarettes must take into account information from all available sources, including clinical reports, and must identify and evaluate the uncertainties and gaps. Animal studies, however elaborate, are only part of a much larger picture and cannot in themselves resolve the issue.[6]

Human Health Effects

Illustrative Case Report

An 18-year-old female college student was admitted to a local hospital in May 1985 with an initial diagnosis of acute pneumonia. Her medical history included a single episode of

TABLE 2.—*Some Known Effects of Eugenol**

Effect	*Exposure*	*Degree of Effect*
Anticonvulsant activity following electroshock	211 mg/kg IP, mice	Potent; transient
Anesthetic	200 mg/kg IP, mice	Potent, dose-dependent
Inhibition of neuronal transmission	0.01%; isolated	Potent; reversible within 3 h
Inflammation	0.1 ml, 100% solution SC, rat	Affected by additives
Sensitization	0.5% to 10% topically, guinea pig	Weakly sensitizing
	0.1% intradermally, guinea pig	Weakly sensitizing
	5% patch test; 155 patients with contact dermatitis	2.6% had allergic reaction
Hypertension, redistribution of regional perfusion, and reduced myocardial contractility	0.05 ml or more IV, dogs	No change in heart rate or electrical activity

IP=intraperitoneally, IV=intravenously, SC=subcutaneously

*From Guidotti et al,[2] Vishteh et al,[9] Hume,[10] Kozam,[11] Isaacs,[12] Rasheed et al,[13] Cotmore et al,[14] Barkin et al,[15] and McCarter.[16]

Figure 4.—Left, A chest roentgenogram at the time of admission to hospital shows dense pneumonic infiltrates in the right lower lobe. **Middle,** A chest roentgenogram taken 17 days later shows several air-fluid levels (cavities), a dense infiltrate in the right lower lobe, and partial clearing of the lateral aspect of the right lower lobe. **Right,** A chest roentgenogram taken 24 days after the initial film shows a large abscess in the right lower lobe.

seizure at age 2, pneumonia diagnosed at age 3, and mild thoracic scoliosis noted at age 10. There was no history of epilepsy, alcohol abuse, bulimia, dysphagia, aspiration, recurrent pulmonary infections, or immunodeficiency disorders. She had smoked an average of two cigarettes per day for six months, including an occasional clove cigarette "for a change." She said she did not use alcohol or drugs except for a few instances of experimenting with marijuana. She said she had not taken any other form of drugs or any medication. About two weeks before her present ailment began, she noted a sore throat, cough, anorexia, and malaise. Most of her symptoms resolved over several days without specific treatment. After completing her university examinations, she drove home to her parents and went to bed around midnight after eating a cheese sandwich. Just before retiring, she smoked a single clove cigarette in her bedroom and, within an hour, she had nausea and vomiting. The next morning, she was lethargic and acutely ill with severe nausea, vomiting, fever, and cough with streaky hemoptysis. She was taken to the local hospital in the evening when the family returned and found her still in bed, feverish, and somewhat incoherent.

On admission, she was observed to be in a toxic condition and in acute respiratory distress with a temperature of 38.8°C (102°F). Minor epistaxis, severe cough, diarrhea, and abnormal lung sounds in the right lower lobe were noted by the admitting physician. The total leukocyte count was 47.5×10^9 per liter (47,500 per μl) with 0.93 polymorphonuclear leukocytes. A sputum Gram's stain showed gram-positive cocci, but culture of sputum and blood specimens showed no growth. Serum titers for antibody against *Legionella* species were negative, as were cold agglutinins and a mononucleosis spot test. An initial chest roentgenogram showed a pneumonic infiltrate in the right lower lobe (Figure 4, left). A presumptive diagnosis of pneumococcal pneumonia was made, and she was treated initially with a regimen of intravenous cephalothin sodium, tobramycin, erythromycin, and corticosteroids. About a week later, her temperature had returned to normal and the total leukocyte count was 13×10^9 per liter (13,000 per μl), but the progression of the pneumonic process on a chest roentgenogram (Figure 4, middle) had prompted the addition of nafcillin sodium and clindamycin. Despite aggressive and clinically appropriate management, the pneumonic infiltrate evolved, on the 24th day after admission, into many areas of cavitation involving the right lower lobe (Figure 4, right). A computed tomography of the chest confirmed the multilobulated areas of cavitation (Figure 5).

On the 29th hospital day, she was transferred to the Mayo Clinic (Rochester, Minnesota) for definitive treatment of the right lung process. An examination disclosed that the patient was afebrile, stable, and coughed intermittently with the production of small amounts of yellowish sputum. Increased vocal fremitus and a combination of bronchial breath sounds and diminished lung sounds were noted in the right lower lobe area posteriorly. There was no lymphadenopathy or hepatosplenomegaly. Blood tests showed the following values: hemoglobin, 6.33 mmol per liter (10.2 grams per dl); total leukocyte count, 10.1×10^9 per liter (10,100 per μl) with 0.75 neutrophils, 0.11 lymphocytes, 0.08 monocytes, and 0.05 eosinophils; and an erythrocyte sedimentation rate of 102 mm per hour. A blood gas analysis while the patient breathed ambient air showed the following: arterial oxygen tension 87 mm of mercury, carbon dioxide tension 42 mm of mercury, and pH 7.41. A sputum culture was negative. On bronchoscopy there were no endobronchial abnormalities, and protected catheter brush specimens were also negative for bacterial growth. Treatment with cefazolin sodium, mez-

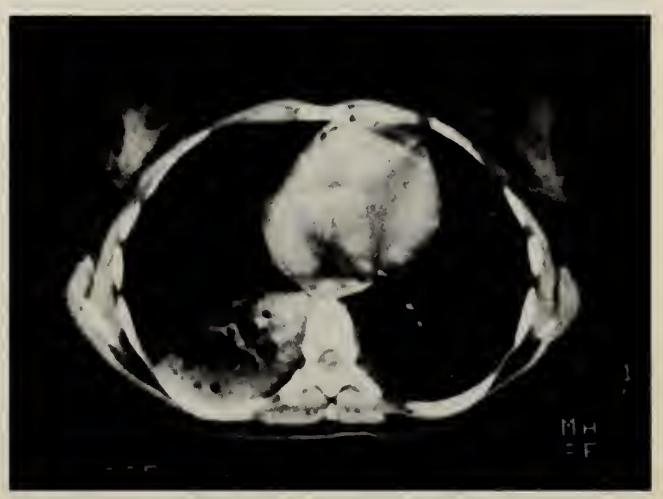

Figure 5.—Computed tomography of the thorax shows a pneumonic process in the right lower lobe posteriorly with many air-fluid levels.

locillin, clindamycin, and chest physiotherapy was continued, with no further drainage or resolution of the abscess cavity. A right lower lobectomy was done, from which her recovery was uncomplicated. Following discharge, the patient steadily regained most of her strength and stamina but notes a diminished reserve on strenuous exercise.

The resected right lower lobe revealed many abscess cavities with adjacent areas of organizing pneumonitis (Figure 6). On histologic examination there was a thick-walled abscess cavity with necrosis of the cavity wall with adjacent areas of alveolar atelectasis and intra-alveolar macrophages (Figure 7).* There was no evidence of granulomata or vasculitis. Special stains were negative for fungi or other organisms, and culture of the resected lung specimen showed no growth of organisms.

Comment

In all, 13 cases of severe illnesses possibly associated with clove cigarette smoking were reported to the Centers for Disease Control and the California Department of Health Services by mid-1985 (Table 3).† Eleven were presented in the early published reports.[1,2] The first case in which an association with clove cigarettes was suspected was recognized by Frederick G. Schechter, MD, of Whittier, California, who continues to make important contributions to our understanding of this issue. The 13th case is that of a 20-year-old woman in Hawaii in whom bronchospasm developed hours after she smoked a clove cigarette, but the condition resolved itself. Details on that case are sketchy, as it was not fully investigated (J. W. Stratton, MD, California Department of Health Services, oral communication, March 1988).

The predominant clinical characteristics among the reported cases (Table 3) have included acute hemorrhagic pulmonary edema or an extensive pulmonary infiltrative process resembling the adult respiratory distress syndrome, followed by death in two. Acute respiratory disorders of this type are extremely rare in previously healthy young people. Even though the mechanisms for the pulmonary disease are not understood, the following should be considered: Eugenol is known to diminish lymphocyte response, macrophage

*The pathologic and histologic details were provided by Herbert M. Reiman, MD, Section of Surgical Pathology, Mayo Clinic, Mayo Foundation, and Mayo Medical School, Rochester, Minn.

†James W. Stratton, MD, and James Collins, MD, of the California Department of Health Services provided useful information on cases identified to date.

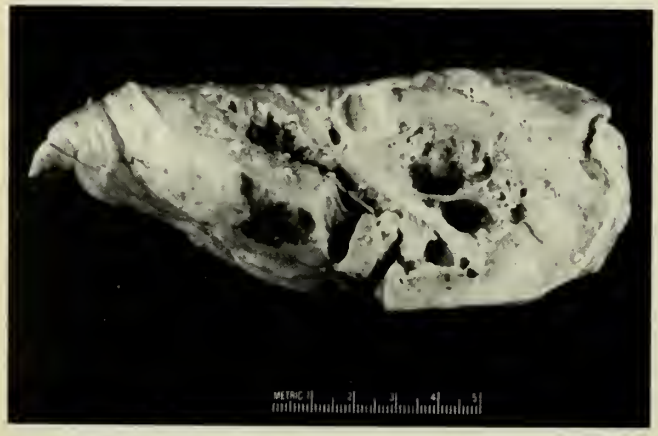

Figure 6.—The gross appearance of the resected right lower lobe shows cavitated abscess formation and adjacent organizing pneumonitis.

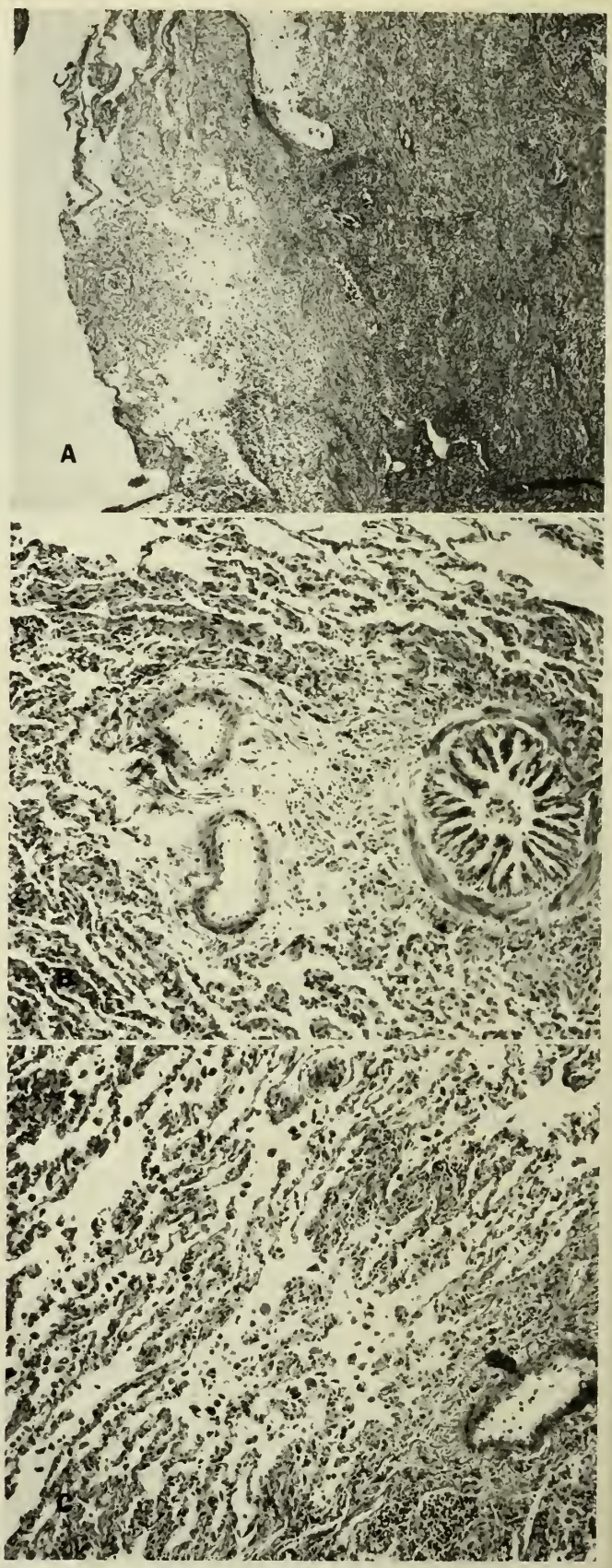

Figure 7.—**A,** The wall of an abscess cavity is shown, with necrosis of the wall and organizing pneumonitis in adjacent lung tissue (× 64). **B,** Essentially unremarkable small bronchiole and pulmonary vessels are seen in atelectatic lung and the area of pneumonitis (× 160). **C,** Intra-alveolar macrophages are shown that may be due to the adjacent pneumonitis (× 160; all three slides were stained with hematoxylin and eosin).

TABLE 3.—*13 Suspected Cases of Adverse Health Effects Due to Clove Cigarettes*

Clinical Characteristic	*Cases, No.*
Sex distribution, male:female	8:5
Median age (range), yr	18.5 (11-35)
Antecedent conditions	
Upper respiratory tract infection	5
Asthma	2
Presentation	
ARDS-like symptoms	5
Infection	3
Bronchospasm	2
Aspiration	1
Other	2
Outcome	
Resolved	7
Died	2
Lobectomy	2
Problem persists	1
Lost to follow-up	1

ARDS = adult respiratory distress syndrome

function, and neutrophil chemotaxis in animals.[9] Smooth muscle contraction is inhibited by eugenol,[10] and it may interfere with the tracheobronchial mucus-clearing mechanism and thus stimulate retention of secretions and subsequent pneumonia. Eugenol is known to diminish the contractile force of cardiac muscle, but no direct cardiac toxicity has been found.[20]

Other mechanisms that may interfere with the respiratory function include depression of the central nervous system[11,12,18,19] and respiratory inhibition by an uncoupling of oxidative phosphorylation and inhibition of the cyclooxygenase pathway.[13,14,19] The rapidity with which the pulmonary disease developed in the reported cases, however, argues against these factors being primarily responsible for the acute pulmonary process. Although the possibility exists of these mechanisms in prolonged illness, it was unlikely, at least in our patient, because there have been no reports of chronic pulmonary disease following clove cigarette smoking. The clinically significant factors most likely to be responsible for the pulmonary disease include the potential of eugenol to irritate the bronchi directly, with resultant hemoptysis, direct alveolar damage leading to hemorrhagic pulmonary edema, and aspiration pneumonia as a result of eugenol-induced pharyngolaryngeal anesthesia, nausea, and vomiting. In two other cases,[1,2] as well as in our patient, the clinical picture strongly suggested aspiration pneumonia; these three patients are known to have smoked clove cigarettes before going to bed, and their histories were highly suggestive of aspiration. The deglutition and swallowing response in humans is a complex mechanism, easily interfered with by factors that alter local reflexes, voluntary swallowing, and pharyngeal sensation. The topical anesthetic effect of eugenol is likely to have such effects.[6]

In another case, acute epiglottitis occurred, showing the potential for upper airway lesions to occur that may be associated with the possibility of aspiration. Hemoptysis to a minor degree and bronchitis are also frequently reported by clove cigarette users,[1] likely the result of direct irritation of bronchial mucosa by clove cigarette smoke. Life-threatening acute toxic effects appear to be uncommon, given the number of users, and may reflect the presence of other factors; several patients are known or thought to have had viral infections preceding the event. Our patient had an antecedent viral-like illness and streaky hemoptysis.

The sporadic and infrequent occurrence of a major pulmonary effect of kretek smoke on the lungs of young adults might also be explained by a previous sensitization to eugenol. Eugenol is known to modify cellular immune responses and to induce allergic reactions in sensitized persons.[15,16] Available clinical evidence suggests that the major acute adverse health effect of kreteks is an idiosyncratic or hypersensitivity-mediated inflammatory process, occurring infrequently and unpredictably following normal use. The sporadic nature of the reports suggests that host factors may play a role in determining individual susceptibility. Nevertheless, clove cigarettes are unequivocally a health hazard to all users. They are tobacco-containing cigarettes, and the health hazards associated with smoking are well known.

The long-term effects of smoking clove cigarettes above those caused by the tobacco are unknown. Cancer and chronic lung disorders are the most likely candidates, but the risk of either cannot be evaluated directly because the fad is too new. The possible cancer risk associated with clove cigarettes, above that of conventional cigarettes, is not known. The International Agency for Research on Cancer has reviewed the evidence for the carcinogenicity of eugenol and has concluded that there is limited evidence for an effect in animals but that no epidemiologic data are available to evaluate the possible risk to humans.[8] Tests of eugenol in short-term assays of potential carcinogenicity suggest that the compound may be active in cell types more closely resembling mammalian cells but not in bacteria. Because previous assays for mutagenic activity were done in bacterial systems, such findings contradict early negative reports and have implications for human exposure.[2,8] The appropriate studies in animals have not yet been done. What is known regarding this family of compounds is disturbing, however. Eugenol is closely related to safrol, a weak hepatic carcinogen. Methyleugenol is a suspected carcinogen in animals where studies suggest the potential of eugenol to be a human carcinogen even though eugenol, as used in dentistry and as a spice, has not been shown to cause cancer.[8] The essential issue is whether the risk to health that its use in smoking confers is substantially greater than that of conventional cigarettes. Studies in Indonesia, where clove cigarettes have been used for many years, have not been done and would be of questionable usefulness, both because of differences between the health reporting systems of the two societies and because the nearly exclusive use of clove cigarettes there would make comparisons with other smoking habits difficult.

Behavioral Effects

Much of the concern about clove cigarette use is related to the spread of the habit among subgroups of adolescents who are highly subject to peer influences and prone to experiment with tobacco and other substances. The early experiences that condition later cigarette smoking habits have not been well studied, in part because any such study would of necessity require at least the passive tolerance of young people smoking. In the absence of meaningful data beyond consumption patterns, we might expect that clove cigarettes would engage young smokers in the habit more easily than conventional cigarettes. The exotic appeal, strong aroma, and peer interest in the product would be factors, especially

given the early image of clove cigarettes as a healthy alternative to conventional cigarettes.

The clove cigarette is nearly ideal in design as a "trainer" cigarette for capturing young people as smokers. This has serious implications for the future smoking habits of users. Behavioral effects may be direct, as in the possible central effects of eugenol, or indirect, as they influence health-related behavior. Both may play a role in any effect of the clove cigarette habit on cigarette smoking when the subjects are young. The initial smoking experience with clove cigarettes is not always pleasurable to mature adults because the taste and odor are overwhelming. Adolescent users report that they prefer clove cigarettes to regular ones, however, and that they perceive clove cigarette smoke as smoother, despite the perceived harshness of the tobacco used and the higher content of tar. The effects of eugenol may also blunt the aversive conditioning associated with the initial response to ordinary cigarettes. Drugs that produce mild euphoria or other pleasurable effects could condition a more compulsive smoking habit. A single clove cigarette may deliver a substantial amount of eugenol to the alveolar surface, where absorption into the bloodstream is rapid and efficient. The central pharmacologic effect of the nicotine, possibly modified by an effect of eugenol, could be pleasurable to immature youths. As a "safe" and easily accessible alternative to marijuana and hard drugs, clove cigarettes may be a titillating way for adolescents to appear daring and "in" with their peer group without taking what they might perceive as the greater and frightening risk of illicit drugs. Our patient, discussed earlier, was introduced to clove cigarettes by a fellow dormitory resident at university seven months before her illness. She obtained a package of 20 clove cigarettes in a local shopping mall for $2.50. Her smoking habits started with her entry into university, where she was a good student and moderately athletic. She was evaluated as having good self-esteem and had no history of marginal or antisocial behavior. No reports of a physical or aberrant psychological dependence on clove cigarettes have yet appeared.

Few studies have examined psychological variables in relation to adolescent smokers. Palmer studied 3,000 junior high school students in South Dakota and Iowa in 1965[27] and found that for adolescents or preadolescents the first experience with smoking seemed to be the crucial one. Solitary experimentation was rare, especially among those who became regular smokers. By age 12, most boys who wanted to smoke had already done so, and among girls, most had tried by age 14. Most of Palmer's subjects reported feeling "nothing" when they smoked their first cigarette. Those who became regular smokers more often reported that they enjoyed smoking, but those who remained only experimental smokers expressed feelings of sickness or shame. Hunter and colleagues found that the number of people who smoked in a child's environment seemed to influence trial behavior, as did beliefs about the rewards of smoking.[26,28] About half of those who started smoking before age 12 smoked their first cigarette with a family member or an old friend. After age 14, the initial experience occurred more often with peers. We might therefore predict that the faddish nature of clove cigarettes may enhance the social influence of experimentation, and the more acceptable taste and anesthetic effect of clove cigarettes may make the first experience with smoking more enjoyable.

Bewley and co-workers confirmed the importance of the initial cigarette experience on later behavior.[29] Of the current smokers, 21% reported enjoying their first cigarette; only 3% of the nonsmokers reported that they expected to enjoy their first cigarette. Two thirds of the nonsmokers expected to be sick. Only 32% of the smokers reported feeling sick on their first encounter, however. Young people with a lower threshold for nausea induced by nicotine are more likely to have an aversive sensation on first smoking and may seek a more acceptable initial experience. Clove cigarettes may spare this group the aversive initial experience they might otherwise have with their early smoking experiments.

Robinson and associates characterized clove cigarette use among adolescents in northern California as part of a larger pattern of substance use, social maladjustment, and maladaptive behavior.[3] They found that two of the strongest predictors of substance use among adolescents were peer social pressure and an attitude that cigarette smoking is acceptably safe. They reported that peer social pressure and a dismissive or rejecting attitude toward the health consequences of smoking were correlated with levels of substance use. Both factors are operating in the case of clove cigarettes.

The false image of the product as clean, natural, and safer than conventional cigarettes seems to attract some young people who would otherwise not start smoking and who are not part of the subgroup of adolescents with problem behaviors. The strong identification of clove cigarettes with trendy music, youth-oriented life-styles, and the exotic adds a cultural dimension of group behavior and peer pressure among young people. How this initial, strongly positive encounter with cigarettes will affect their later smoking habits is a matter of conjecture. No studies are known to be underway to document such an effect. This is doubly unfortunate because such studies might help us to understand the motivations and practices of young smokers just starting the cigarette habit in general as well as the dynamics of clove cigarette use.

Regulation and the Media

Reflecting an early local recognition of the fad, the American Lung Association of San Diego and Imperial counties was the first agency to issue a public statement on the possible health risks associated with clove cigarettes. This was part of a 1982 policy document on cigarette additives.[5]

In December 1988, the Council on Scientific Affairs of the American Medical Association released its own review of the evidence for health effects. The report recommended that "since the American Medical Association has an existing policy vigorously opposing the use of any tobacco product, this policy should now be extended to include explicit opposition to the use of clove cigarettes. Further, it is recognized that smoking clove cigarettes may present an additional hazard to susceptible individuals."[30]

The fad received considerable publicity in the national media in 1984 and 1985 because of the concern over acute ill effects. In addition to heavy coverage by local news media, particularly in southern California, articles appeared in several national publications, including *Time* magazine ("Clove Smokers: Danger in a Teen-age Fad?" January 17, 1985, p 63), *The Wall Street Journal* (S. P. Galante: "Clove Smokers: Pure Puffing or Health Hazard?" June 3, 1985, p 23), and *Consumer Reports* ("Beware Those Spicy Cigarettes," November 1985, p 641), and the issue has been broadcast on network radio and television, including the NBC "Today" show and "Good Morning America." Sales of the cigarettes

have fallen in this country since the beginning of 1985, when publicity over the risk to health reached a high point.

The Specialty Tobacco Council is an organization of the principal manufacturers and distributors of clove cigarettes. Based in North Carolina, with an information office in Los Angeles, this organization has distributed information representing the industry's point of view to the media, has represented the industry in legislative matters, and sponsored the Huntingdon studies, reportedly anonymously to avoid charges of bias. The Specialty Tobacco Council maintains a professional staff and legal counsel and has been aggressive in challenging those calling the safety of clove cigarettes into question.

In the United States, regulatory options for tobacco products are limited. These products are not subject to the same requirements of safety and quality control as food, cosmetics, or drugs. The advertising of all tobacco products (including clove cigarettes) is regulated by the Federal Trade Commission, and each packet must carry the Surgeon General's warning. Since October 1985, the US Department of Health and Human Services has required manufacturers and distributors of tobacco products to report any additives, including natural materials such as cloves, so that it can monitor threats to health. There is no federal legislation that authorizes the restriction of imports or a nationwide banning of sales of a tobacco product, even in the face of a demonstrable hazard to health. The federal government has only the most tenuous authority over tobacco products.

New Mexico, Maryland, Nevada, and Utah have banned the sale of clove cigarettes. Other states have considered such a ban. In Florida a ban was overturned on constitutional grounds after it was passed by the legislature. In California, where the fad began in North America and where it still appears to be most entrenched, the legislature chose not to ban clove cigarettes—as provided for in Assembly Bill 2559, 1985—but to appoint a scientific advisory board to review the evidence and to advise the legislature on possible adverse health effects (Assembly Bill 2559, enacted, October 1985). That board has now completed its deliberations and in October 1988 recommended "strongly" a complete ban on their sale in California as "the most practical and most effective way" to deal with the problem.[31] The board observed that there was no substantial issue of balancing costs against benefits because there were no health or social benefits of consequence to be considered. The role of the states in this matter is complicated by several factors, including the jurisdiction of state and local governments in this area of primarily federal concern, the degree of hazard of clove cigarettes compared with that of ordinary cigarettes (a proven lethal commodity), and the validity of the concept of informed assumption of risk that underlies US regulatory policy with respect to tobacco products, particularly as it may be construed in relation to products consumed by teenagers. The issue of clove cigarettes, far from being a unique and transient concern, has raised fundamental questions about the regulation of tobacco products.

Conclusions

There is not much known for certain about the health effects of clove cigarettes. Given the decline in popularity of the product, it is entirely possible that important issues may never be resolved. For purposes of public policy and the protection of the public interest, however, the following conclusions can be drawn:

- There is evidence to suggest that some persons may be at risk for rare but severe respiratory effects. A larger proportion of users may experience minor health effects, particularly hemoptysis. The characteristics that might predict the occurrence of these outcomes in a healthy adolescent are unknown.
- The indirect effects of clove cigarettes may involve mild central effects, behavioral aspects of using the product, and the local anesthetic effect of eugenol on the upper airway. They are likely to have the effect of conditioning a later smoking habit among adolescents who use clove cigarettes to initiate their experiments with smoking.
- This product has been associated in the past with questionable sales practices that have had the effect of promoting smoking among adolescents. The products have also had a misleading image of safety and "herbal" properties.
- The long-term effects of the product cannot be evaluated because of the short duration of the fad in North America and Australia and the impossibility of controlling for the many other influences on health studies in societies where clove cigarette use is common. The carcinogenic potential of clove cigarettes is apparently at least as great as that for conventional cigarettes.
- Given that clove cigarettes are an utterly dispensable habit, carry a risk at least as great as that of conventional cigarettes, and are most heavily used by young people at risk of incurring a permanent smoking habit, the use of the product should be discouraged. Whether a legislated ban is appropriate depends on the regulatory philosophy, jurisdiction, and legal authority of a state.

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Lessons From the Practice

A Matter of Trust

LOUIS BORGENICHT, MD, *Salt Lake City*

My last patient on a recent Monday was a new patient, a last-minute addition.

"Am I finished?" I asked my secretary.

It was nearly 6 PM, and I had started packing my panniers for the bike ride home.

"You have one more patient coming right in. I tried to get them to see someone tomorrow, but they wanted to see you today. They're friends of one of your patients."

I sat down to wait, wondering what sort of problem would bring a new patient in at the very end of the day. Why did they have to see me? My ego hung on the edge of curiosity.

A few minutes later Lianni, Peter, and Tami arrived, signed in, and were put in an examination room. When I entered the room, I recognized the father. He worked at a recreational supply store that I frequented; last week I had bought a pair of hiking boots from him.

The story was simple: ten days earlier Lianni, now 9 months old, had developed symptoms of a clear runny nose and a cough. Having planned a vacation for several months, the family flew to Wisconsin as scheduled on what I suspected was a nonrefundable ticket. She had "seemed very uncomfortable during the flight." Three days later Lianni was sicker with fever. Her parents took her to a holistic doctor who diagnosed "red ears," prescribed a regimen of pulsatilla and garlic oil, and suggested that they not fly home because of the possibility of further damage to her ears. The family then rented a car and drove back to Salt Lake City. The cost for the car rental alone was $650. I also wondered about the stress of driving across country with a sick child. During the drive Lianni's right ear had started draining. They were in my office now for the opinion of a pediatrician.

Lianni did not appear very ill. She was comfortable in her mother's arms, not crying or irritable. Even during my examination she remained unperturbed. She was breathing slightly faster than normal, had mild wheezing, and had a middle ear infection in her left ear. Her right eardrum was perforated.

This was an unequivocal medical situation: an obvious purulent middle ear infection on both sides with a perforation on the right from pressure in an enclosed space. It was entirely possible that the ruptured eardrum had been a therapeutic response to a pathologic situation, maybe even curative.

The four of us went into my office to discuss the next step.

"Sounds like you had a tough week. Lianni's ears do not look good. It's the kind of situation that I would treat with antibiotics, probably amoxicillin. Let's talk about it."

"What would happen if we didn't use amoxicillin and just continued the herbal remedies?" Tami asked.

"I don't know, but I can understand your hesitancy. We don't know how many ear infections would clear up on their own without antibiotics. We never let them get that far. We always treat them. I suppose the only way to know scientifically would be to culture the middle ear fluid of kids with clinical ear infections. When it's been done, maybe 20% to 30% are viral and might clear up on their own, but you never know. So we just treat and thus probably overtreat."

Peter asked, "What might happen? What complications could she get?"

"Back in the days before antibiotics we used to see serious complications from ear infections—like mastoiditis, meningitis, brain abscesses. I actually saw a child years ago when I worked on an Indian reservation who had a brain abscess as a result of having a chronic and untreated ear infection with a wide perforation that never healed. But that is not Lianni's case. We'll watch her closely no matter what we do."

Peter and Tami thought for a minute. Lianni was getting fussy, wanting to nurse.

"Let's go home and talk it over," Tami said.

I interrupted, "Let me give you this amoxicillin prescription anyhow in case you decide to use it. I would like to know one way or the other, so please call me with what your decision is. In any case, I would like to check her ears in two weeks to see how things look."

They paid at the front desk and were gone. I thought the visit had gone well but really did not have a good sense for what their decision would be. They would clearly do only what they wanted to do because they were intelligent, concerned, independent parents who had resisted dealing with allopathic medicine until a naturopath in Milwaukee had suggested it.

I suppose I was not surprised when they had not called two days later.

Exactly two weeks from the first visit, the family returned for a recheck. They had not filled the amoxicillin prescription but had used herbs with antibiotic properties orally and in the ears. Lianni's ears were better but not entirely normal. They appeared dull instead of the normal translucent grey and did not move at all—evidence of persistent fluid behind the eardrum. The original perforation had healed with a thin membrane.

We were all relieved.

"If this were the usual case, I would opt for a change of antibiotics and a recheck in two weeks. So it might be good to use a slightly different herbal regimen," I said.

By now I was intrigued not only by the parents' commitment to Lianni's health but also by the seeming cure. Lianni's

(Borgenicht L: A matter of trust. West J Med 1989 Aug; 151:229-230)

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ears were better. Maybe they just needed more time. We all agreed to follow up in two weeks.

The final visit went as scheduled. Lianni's ears were absolutely normal. There was no evidence of scarring, fluid, or perforation on either side.

Maybe we had simply been lucky. This was only one of perhaps 300 or more ear infections I would see this year. In the end I was left with more questions than answers. Would most of my colleagues trained in allopathic medicine have been uncomfortable with the open-ended situation at the end of our first visit? Should I have been more authoritarian and directive? Should I have said that I would refuse to see them if they did not comply with my suggestion for antibiotics?

I was interested in the fact that Lianni's ear infection had cleared so completely with the aid of herbal remedies. I will never know whether it would have improved without any therapy. On the other hand, I have seen ear infections persist despite treatment with a series of antibiotics—two weeks each of amoxicillin, trimethoprim-sulfamethoxasole, and cefaclor.

None of this musing has changed my therapeutic approach to this common problem. What I had done was to be there as a support and resource should Lianni have gotten sicker. My uneasiness with the situation never surfaced consciously until she was cured. It was kept in control during my contact with her family by a sense of trust: I trusted the family to return if there was a problem; they trusted me not to reject their unorthodox approach. Maybe that was what made the difference.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Gold

PARENTERAL GOLD is sort of the tried and true drug that has been available for years. There's an interesting sort of side story on intramuscular gold—how it ever got started to be used. Back in the 1800s many diseases were thought to be due to infections. Infections were treated with heavy metals—syphilis, as you know, was treated with arsenic compounds. Rheumatoid arthritis was suspected to be due to tuberculosis, which was thought to be curable, or at least treatable, by gold salts. As a result, people with rheumatoid arthritis started being given intramuscular gold salts and, in fact, they did get better. We now know, or at least we think we know, that rheumatoid arthritis is not caused by tuberculosis. An interesting thing is that when people have studied it, the tubercule bacillus is, in fact, inhibited in growth in vitro by gold salts. So, it's an interesting medical-historical phenomenon. Nobody knows exactly why it works.

—PAUL A. FEIGENBAUM, MD

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Book Review

The Second Medical Revolution—From Biomedicine to Infomedicine

LAURENCE FOSS and KENNETH ROTHENBERG.
New Science Library—Shambhala, 314 Dartmouth St, Boston, MA 02116, 1987. 313 pages, $29.95.

AT FIRST GLANCE the title of this book may seem audacious, but the word revolution is not to be taken lightly. While not negating the miracles that medicine has achieved during the past 300 years (since the first revolution of scientific medicine) nor the necessity to gain basic knowledge at the atomistic level, the authors will propose that the biomedical model that supports modern day medicine be subsumed under a more comprehensive scientific successor—one that will address the increasing need in the health care system to factor in the "extrasomatic" variables (social, ecologic, and psychological).

Like the proverbial men from Mars, the authors are curious about a perplexing incongruity: that medicine, the most humane of the sciences, continues to negate or treat as an anomaly—at best a "risk factor"—these eminently human variables. They propose to include them in a new model deriving from the conceptual ideas of 20th century (postmodern) science. They will call their new model "infomedicine."

Both bring to this formidable challenge no built-in prejudice, for they are not medical scientists nor health care practitioners. They are scholars: Foss in the philosophy of science and organizational development and Rothenberg in education. Their writing is articulate and examples relevant, timely, and valid. Their tables are clean and their figures helpful and easily understood. While to some their classroom-type presentation may seem redundant, the complexity and scope of the material—philosophical, scientific, and pragmatic—and the necessary dialectic method of approach support this comprehensive, step-by-step method.

The book is a painful pleasure to read. A pleasure because the authors create an ambience of intellectual grace that liberates the imagination toward philosophical and clinical gratification. Painful because of the continuing necessity to extricate oneself from the all-encompassing causal mode of description that has habituated medical thinking. This causal mode has come to stand for scientific and medical explanations and dominates our language, nosology, and explanations, always promising that, logically, some day all phenomena, including the extrasomatic anomalies, will be reduced to physical mechanical explanations. Paradoxically, we seem to sit and wait while knowing *a priori* each moment that daily human existence is a dynamic, constantly emerging, self-renewing, irreversible phenomenon. It was a humbling experience for me to see how resistant I was to allowing these exciting new ideas to nudge aside the tenaciously held old ones.

The book is divided into four parts: The First Revolution; The Prelude to Revolt (the Insurgents); The Second Revolution: Post Modern Sciences; and The Revolutionary Thesis: Infomedicine.

The introduction itself is a concise and comprehensive treatise and will provide the browser an excellent overview. The intellectually curious, however, will be drawn into the body of the argument and in all probability will explore selections from the broad and up-to-date bibliography.

As a framework for their presentation, the authors propose a three-tiered conceptual model. At the foundations level (tier one) are the philosophical ideas and concepts, such as reductionism or determinism, by which science approaches the world and makes enquiries. These ideas inform tier two, which consists of the basic disciplines of medical science (molecular biology, for example) which in turn support tier three, the medical strategies, research technologies, and practice, such as pathophysiology. They will argue that each of these tiers feeds and reinforces the others in a loop arrangement and, surprisingly, that the informing model itself creates its own self-restricting world view as does a fixed lens. Hence, "the generally accepted foundations of medicine determine the questions to be asked, what methods are used to answer the question, what counts as an answer, and, finally, whether the question-and-answer session was a success." Thus, any notable change in principle or practice (tier two or three) will not and cannot take place until and unless there is a substantial change—or revolution—at tier one. Following this scheme, the authors will first "unpack" the present medical sciences model and expose its limitations scientifically and logically in today's health care environment. Subsequently, they will build up the new revolutionary model from emerging new data. This historical survey makes delightful reading and reveals the pervasive influence of the traditional natural science (Newtonian) concepts and the continuing tenaciousness of the conundrum of Descartian mind-body dualism that holds that "were there no mind at all, the body would have the same function."

This overview concludes with a delightful exploration of the epistemologic puzzles of two popular "research" cases: Norman Cousins' self-cure (Smith A: Mind, body and laughter: Can a change of attitude cure dread disease? Esquire, Feb 1980) and the 'placebo' psychodynamics of pain control and endorphin functions.

Part two details the emergence of a variety of countermovement disciplines from within the medical enterprise itself. These "insurgents" have brought overwhelming data to show causal relations between the extrasomatic variables and the disease process. Their fields of exploration naturally divide them into such medical disciplines as environmentalists, holists, and behaviorists. They are united, however, in viewing the patient not as a biologic machine but as an ill person caught up in the interactions of a host of extrasomatic variables. They display accumulating data that are overwhelming in their potency, especially those from current behaviorists, the psychoneuroimmunologists, who have shown direct causal relationships between the mental events of learning and memory discrimination in the T cells of mice that were conditioned to respond to saccharin as if it were a cytotoxin.[1] In addition, a study group supported by the National Heart and Lung Institute reported in 1977 that "what are probably unique human behavioral phenomena must be recognized as causative in coronary disease."[2] Why, the authors muse, in the face of such overwhelming evidence from clinical and laboratory research, did these insurgents settle

for detente with institutionalized medicine rather than forcing a debate at the foundations level of the biomedical model?

Their answer is startling, especially for those who, like me, were a part of this generation. The insurgents themselves were constrained by their own education in the epistemology, language, and nosologies of the natural science model. They, too, were waiting for physical "connections" between mind and body to be exposed. Their interactionists' model, built on the general systems approach of Bertalanffy and brought to its apotheosis by the veteran George Engel, did survive and will be used as the bridge for the revolutionary proposal. Thus Engel's commendatory foreword is of interest: "Once the post-modern scientific principles are in place, neither what is human nor what is ecological can any longer be ignored or excluded by being deemed reducible to something else."

Part three is pivotal and presents the argument that it is a scientific and philosophical blunder, as well as clinically dangerous, to wait for a "causal," physico-chemical explanation of extrasomatic variables. Furthermore, it is not possible to explain anything human at that level. How can something not physical (mind, society) causally "connect" with something physical?

An alternative scientific explanation, however, is both possible and persuasive. Indeterminism, rather than determinism, is at the foundation. The authors ground their conceptualizations in the disciplines of postmodern science—quantum theory, nonequilibrium thermodynamics, geochemical biology, and information theory. These conceptualizations hold that knowledge of the state of the system at any one time will not allow the prediction of the state of that system at any subsequent time. Nor is it reversible or reducible. Furthermore, it is self-organizing, in a steady state kept near equilibrium by the dynamics of positive and negative loop arrangements in which information to activate and modulate is transferred.

Constructing a new model in this orientation, the extrasomatic aspects of human existence can now be viewed as part of a hierarchy of interacting systems arrangements that store, process, and transfer information in an exchange with the physical and social world. Here, linearity and atomistic "connections" are replaced by interacting complementary systems, and the human (patient) is characterized as an information processing mind-body unit in an open systems energy and information exchange with the physical and social world. The disease locus will be described in terms of pathopsychophysiology rather than pathophysiology.

Part four of the book explores the revolutionary potential of this new "info-model," inviting comparisons at various levels with the current model and highlighting how the nature of this foundation's choice will affect every aspect of medical philosophy and practice, from concept of disease to patient relationship and appropriate therapy choices.

Since both models claim internal consistency and scientific integrity, the authors test them first one against the other using a clinical syndrome, atherosclerosis, and later against two hypotheses: prednisone increases cholesterol, and mental events cause disease. In the testing discussion there is a beautifully articulated and scholarly exposition of the nature of causality—determinism versus indeterminism—and of validity (proof). In passing, Foss and Rothenberg clarify the Cartesian concept of dualism and answer the charge arising from a spate of articles in the *New England Journal of Medicine* from 1983 to 1985 that, paraphrased, claimed that we have been too ready to accept the venerable belief that mental states are important in the causes and cure of disease, that such data are mostly folk lore. "We must have proof," the authors of these articles urged, "at every level of connections."[3,4]

Of particular interest even to the browser is the concept of isomorphism, set forth here as an example of the ubiquitous presence of information in all of nature. Nature, the authors suggest, is parsimonious; previous functions that have proved efficacious are preserved through the genetic code and passed along from species to species (like the function of the secondary messenger cAMP or neuronal organizations and function). Thus the biochemist and the neurophysiologist can explore the nature of memory in a protein that transits the cell membrane of *E coli* or in the dendritic arrangement of the snail and extrapolate their findings to humans. Peptide "messengers" carry information level to level in all species isomorphically, as do humans' symbols person to person. Since no message can be read in isolation, physicians will engage their patients in dialogue and learning as they mutually search for the meaning of certain basic categoric messages.

The concluding chapters of the book are gently polemic, pointing a finger at those forces characterized here as "the invisible college" that resist changes. These include the granting institutions that support research, the massive substructure of the pharmaceutical industry, the fixed required curriculum of medical schools (with no encouragement for reflection), and the nosology and vocabulary of medicine itself that constrains health policy codes.

A primary value of this book is in the intellectual stimulus that continually nudges against the constraints of traditional thought process. My mind creaked and groaned as it held the basic knowledge obtained through reductionistic research and fitted it into the irreversible dynamic process of the new model-as-information. The "noise" was worth the effort. It is required reading for all those acolytes, disciples, and admirers of George Engel and for primary care physicians, whatever their specialty. All health care workers will use it to enhance their ideas of illness as a human event.

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Precautions: *General* — 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests — False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions — No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H_2-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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(Continued on Page 236)

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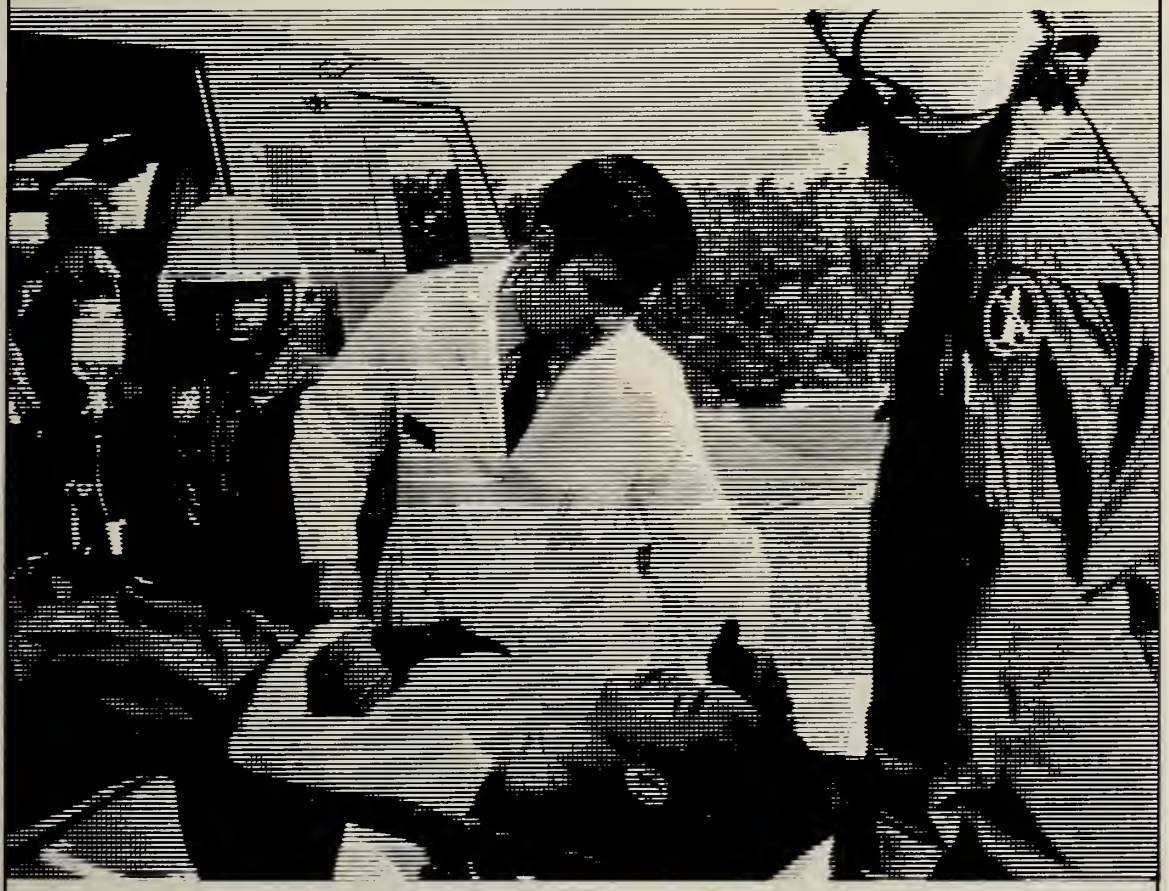

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PEDIATRICIAN. BC/BE physician to join seven member Pediatric department in 55 physician multispecialty group. New medical building with inhouse ancillary services, urgent care center, and surgery center. Competitive salary, excellent benefits including partnership opportunity. Please send CV or contact Susan Smit, Director, Practice Development, Harriman Jones Medical Group, 2600 Redondo Ave, Long Beach, CA 90806; (213) 988-7062.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful ambulatory health care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE primary care specialists preferred. Contact Bob Morris, MD, FACEP, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521: office number (707) 822-3621, ext 191.

UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is in the second phase of an ambitious development plan and is searching for physicians residency trained in Emergency Medicine. The Health Sciences campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level I trauma center, has paramedic base station training responsibilities, and has a helicopter service. Emergency Physicians supervise medical students, interns, and residents in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

(Continued on Page 237)

(Continued from Page 236)

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* statewide. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

BC/BE INTERNIST being recruited for the community of Artesia, New Mexico. Solo practice with cross-coverage available from local Internist. Community-based financial assistance may be available for the right individual. Family oriented community with year round recreation; excellent weather. Fully equipped 38-bed hospital. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, General Surgery, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

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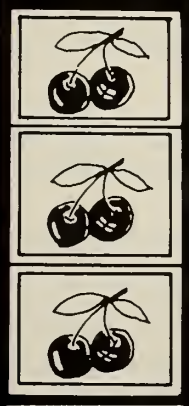

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Prestigious national clinic group specializing in the treatment of venous disorders seeks a highly qualified and experienced M.D. to lead our growing western region practice. We require a minimum of 15 years of teaching, clinical and administrative experience. Must have proven M.D. leadership abilities, interpersonal skills and communication skills. Fifty percent administration (travel)—50% clinical practice mix anticipated. We offer an outstanding salary and bonus potential along with full benefits.

This is a senior level position reporting to the National Medical Director and offers potential for financial and professional advancement with the recognized leader in the treatment of venous disorders. Send your resume in confidence to:

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AMERICAN CANCER SOCIETY®

(Continued from Page 237)

PHYSICIANS WANTED

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee-for-service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

STAFF PHYSICIAN. General/Family Practice. Northern California clinic with large Medi-Cal clientele. Three physicians, two physician assistants. No Obstetrics. No Surgery. Near mountains, close to Sacramento, two and one-half hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Contact Jackie Travis, 938 14th St, Marysville, CA 95901; (916) 741-6245.

PATHOLOGIST. AP-CP to join three BC AP-CP with special competence, certified in Dermatopathology, Immunohematology, and Immunopathology. 300-bed progressive acute care hospital. Adding a fourth Pathologist due to workload. Must have or be willing to develop a forté in Microbiology in addition to sharing AP workload. State-of-the-art medicine. All medical and surgical subspecialties represented. Boise, Idaho's capital city, has an enviable four season climate with abundant recreational outlets. World class fine arts center. Four year college with large stadium and sports pavilion. Downtown parks and river known for float trips and fishing. Six double chair lift skiing 16 miles away. Excellent schools. Great place to raise a family. Competitive income. Desire recently trained individual. All details first letter. No phone calls please. Reply to John C. Day, MD, 190 E. Bannock, Boise, ID 83712.

SACRAMENTO, CALIFORNIA. Part-time, semi-retired Orthopedic Surgeons and Neurosurgeons needed as independent medical examiners. Limited treatment, if desired. Flexibility in scheduling. Lucrative fee-for-service. California license and BC required. Reply to Number 158, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIAN BC/BE. Join two Pediatricians and nurse practitioner in busy, quality practice in rapidly growing community near Sacramento, California. Excellent community hospital and quality of life. Five person call schedule. Send CV to The Childrens Medical Clinic, 729 Sunrise Ave, #602, Roseville, CA 95661.

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

OREGON

Excellent opportunity for BC/BE General Internist with large multispecialty group in Portland metropolitan area. Group provides comprehensive medical care to 350,000 members of established northwest HMO. Position offers wide range of Internal Medicine and ample opportunity for subspecialty consultation within collegial professional environment. Competitive salary and benefit package, including generous pension program, sabbatical leave, and professional liability coverage. Forward inquiry and CV to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227

PHYSICIANS WANTED

PHYSICIANS
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JSA, Inc., an internationally recognized healthcare management and consulting organization, is offering physicians full and part-time positions in a challenging and busy Family Practice/Primary Care Clinic located in San Diego, CA.

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Qualifications include Board Certification in Family Practice, Pediatrics or a Primary Care Specialty, current state licensure and ACLS/BCLS.

For additional information, please contact: Susan Bray, Recruiting Director, JSA, Inc., Box 1305, Columbia, MD 21044. (301) 964-2811.

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MD NEEDS NATIONWIDE. Family Practitioners, General Practitioners, Internal Medicine, OB/GYN, operating room, and other subspecialties needed for private groups and associations. Len Nugent and Co, 1556 Halford Ave, Ste 181, Santa Clara, CA 95051; call (408) 984-8293.

LOOKING FOR INTERNIST/FAMILY PRACTITIONER to join five physician group in Truckee, California. Northern Sierras at elevation 6,000 feet. Abundant recreation summer and winter—beautiful Lake Tahoe, restaurants, and skiing. 40-bed hospital with six ICU beds. Contact R. B. Ganong, MD, PO Box 2649, Olympic Valley, CA 95730; (916) 583-5320.

WESTERN MONTANA. Family Practice Physician wanted to join two physician office practice. Nice, well equipped office. No OB or surgery. Women encouraged to apply. Full-time or part-time. Excellent schools, beautiful area, 25 minutes to major medical area. Reply to Number 163, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST. BC/BE Internist wanted to join Internal Medicine group practice. Competitive salary and excellent fringe benefits. Early partnership. Send CV to Number 162, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602, or call Sara Brenner, (213) 478-5913.

BAY SHORES MEDICAL GROUP

offers an outstanding opportunity for a BC/BE Cardiologist with invasive and interventional expertise. We are an 80-physician multispecialty group practice in southern California, close to ocean, easy access to city and recreational areas, excellent schools. Please direct any inquiries and CV to Bradford B. Burnett, MD, Medical Director, Bay Shores Medical Group, Inc, 3625 Del Amo Blvd, Ste #270, Torrance, CA 90503; (213) 543-7247.

FAMILY PRACTICE, NORTHERN CALIFORNIA. Immediate opening. Competitive salary. Excellent benefits. Malpractice provided. Contact Debra Pahl, CTHP, 564 S. Dora St, Ste D, Ukiah, CA 95482; (707) 468-5341.

BC/BE INTERNIST being sought to establish practice in resort community of Ruidoso, New Mexico. Beautiful mountain setting with easy access to all forms of recreation. Financial assistance may be available for the right individual. For more details, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering professional association or solo practice start-up. Includes attractive income guarantee. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

GENERAL PRACTICE—SOUTHEAST WASHINGTON. 32 physician multispecialty clinic needs full-time physician as second physician in Immediate Care Center. Center is part of main clinic and has full range of ancillary and consultative services available. Abundant free time with no on-call responsibility. Excellent school system. Outstanding recreational and cultural opportunities. Guaranteed salary with excellent fringe benefits. Contact Robert Caudill, MD, or David Maloney, Administrator, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720.

SKI COUNTRY

BC/BE Family Practice Physician wanted for full-time faculty position. Must be willing to do OB. Prior teaching experience preferred. Opportunity to be involved in development of innovative rural health training. Contact **Dr Daniel Dill, 2333 N. 6th, Grand Junction, CO 81501; (303) 244-2195.**

(Continued on Page 240)

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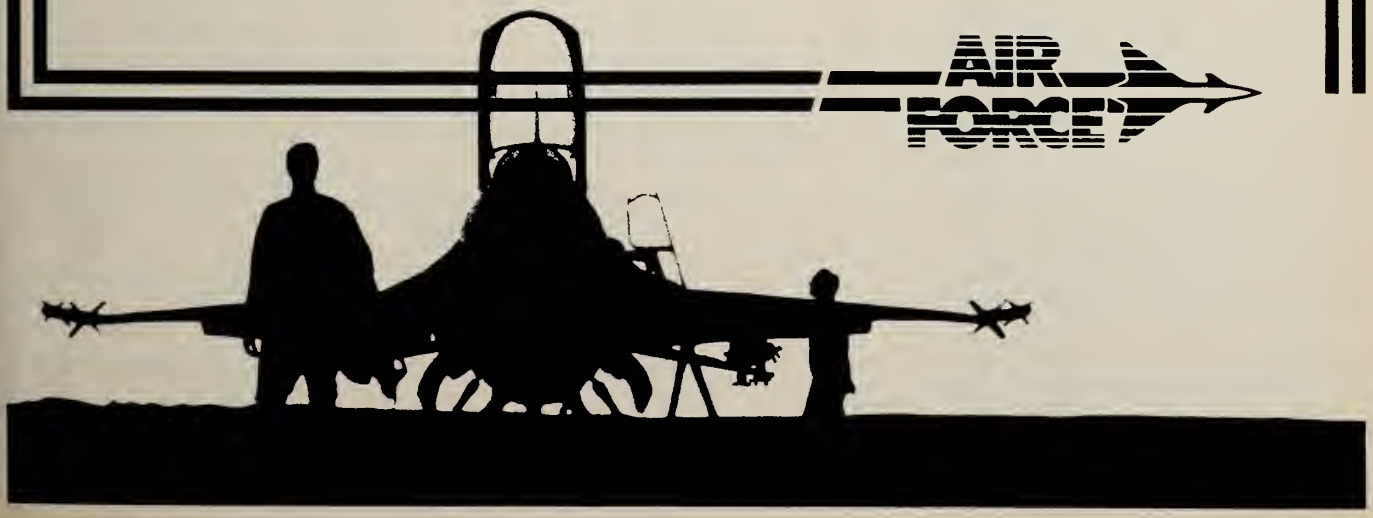

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PHYSICIANS WANTED

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OBSTETRICIAN-GYNECOLOGIST

BC/BE physicians wanted for full-time positions in the Department of Obstetrics/Gynecology in Stockton, California. Our department currently has three physicians and two nurse practitioners. We are looking to add two additional physicians.

Stockton is an attractive community with its own recreational and cultural attractions and is well located within two hours of the mountains, the ocean and the San Francisco area.

Salary and benefits are excellent, including paid vacation, retirement, education leave, medical and dental, and malpractice insurance.

Contact:
Frederic D. Baker, MD
Physician-in-Charge
The Permanente Medical Group, Inc
1305 Tommydon St
Stockton, CA 95210
(209) 476-3013

SOUTHERN CALIFORNIA. Established communities and neighbor with expanding population of 100,000 located one hour east of Los Angeles seeks Gastroenterologist and General Surgeon for private practice opportunities. Outstanding hospital and new ambulatory medical center. Highly competitive practice package. Please call or send CV for full details. Complete confidentiality assured. Contact Ken Baker at (415) 981-7424 (collect). Physician Search Group, 50 California St, Ste 400, San Francisco, CA 94111.

BC/BE GENERAL INTERNIST to associate with growing established Internal Medicine practice in beautiful Sierra foothills. Convenient to Sacramento, mountain resorts, and South Lake Tahoe. Progressive medical community with most specialties represented. Excellent, well staffed and equipped hospital. New medical complex being built in fastest growing area of county. Compensation negotiable. Early partnership. Subspecialties of Infectious Disease or Pulmonary would be welcome. Reply Frank D. Irwin, MD, 3420 Coach Ln #1, Cameron Park, CA 95682.

SACRAMENTO EMERGENCY ROOM. Full- and part-time positions in beautiful river city. Easy travel to San Francisco, Lake Tahoe, and wine country. $100,000 to $130,000 plus a year for 8 to 10 shifts per month. Emergency Room experience, BE/BC, Family Practice, Emergency Room, Internal Medicine. ACLS card current. Mike Kan, MD/Marilyn Juricic, MD, PO Box 15056, Sacramento, CA 95851. CV, references, ACLS copy. Phone (916) 920-0333.

SAN FRANCISCO. Well established General Internist seeks BE/BC associate, private practice, some Geriatric emphasis, benefit package includes incentive options, pension funds, malpractice. Contact Martin Lorber, 1500 Southgate Ave, Daly City, CA 94015; (415) 992-4466.

SACRAMENTO AMBULATORY/URGENT CARE. Part-time openings for Family Practitioners and Internists with experience in adult ambulatory care. Clinic operates 12 hours per day, seven days a week for acute care. Flexible scheduling. Benefits available for physicians working at least six half days per week on a regular basis. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

PHYSICIANS WANTED

PEDIATRICIAN—UTAH. An extremely busy and well established Pediatrician in Layton, Utah, is now seeking an associate. This physician has two offices, one of which is located next to our 110-bed hospital. Layton, located just 20 miles north of Salt Lake City and 15 miles south of Ogden, has a service area of 140,000, 70 percent of whom are under the age of 35 with large families. For further information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-8A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Michael Getzell, MD, Chief, Dept of Internal Medicine, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545.

SAN FRANCISCO. Seeking BE/BC Internist for part-time or full-time locum tenens in busy department of medicine with full subspecialty backup. Excellent salary and full benefits if working six or more half days. California license essential. Contact Paul Feigenbaum, MD, Chief of Service, Kaiser Permanente, 2200 O'Farrell St, San Francisco, CA 94115; (415) 929-2665. EOE.

PRIMARY HEALTH CARE CLINIC serving low- and no-income clients is seeking a physician to join our three Family Practitioner staff. Salary range is $25 to $30 per hour for 10 to 20 hours per week. We are a collective, multiservice nonprofit in a university town near forests, rivers, mountains, and the ocean. If interested, contact White Bird Clinic, 509 E. 13th, Eugene, OR 97401; (503) 484-4800.

PHYSICIANS WANTED

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Pediatrics, General Surgery (breast disease focus), OB/GYN. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Dr Larry W. Hirons, Medical Director
1162 Willamette St
Eugene, OR 97401

BC/BE FAMILY PRACTITIONER sought to join an established practice in Albuquerque, New Mexico. Please send CV to Kathryn M. Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8338.

BC/BE INTERNIST sought to join an established practice in Albuquerque, New Mexico. Please send CV to Kathryn M. Rhoades, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8338.

GENERAL INTERNIST/NEUROMUSCULAR/COPD / REHABILITATION. We are seeking a BC/BE General Internist to join the staff of a 48-bed respiratory unit at an internationally recognized rehabilitation center affiliated with the University of Southern California. Must demonstrate interest in management of respiratory-neuromuscular/chest wall disorders, COPD and tuberculosis. Some critical care. Busy exercise lab. Opportunity in clinical investigation. Clinical faculty appointment at USC, depending on qualifications. Interested individuals should send CV to Ahmet Baydur, MD, Chest Medicine Service, Rancho Los Amigos Medical Center, 7601 E. Imperial Hwy, Downey, CA 90242. Equal Opportunity/Affirmative Action Employer.

WASHINGTON STATE

ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY	HEMATOLOGY/ONCOLOGY
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DERMATOLOGY	RHEUMATOLOGY
INTERNAL MEDICINE	GENERAL SURGERY

FAMILY PRACTICE—permanent, part-time, locum tenens

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
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Spokane, WA 99202
(509) 838-2531

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PHYSICIANS WANTED

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Growing multispecialty group practice
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seeks Board Certified/Eligible:

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- Pediatrician
- Family Practitioners
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- Pulmonologist
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- Internist

We offer competitive compensation and excellent benefits; shareholdership option after 1 year. Located 60 miles north of Los Angeles, our community is one of the most beautiful areas in California, with excellent schools, a strong economy, and a wide range of cultural and recreational activities. Call for more information. Send inquiries and Curriculum Vitae to:

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PORTLAND, OREGON. Two very busy Internists seek third General Internist this year and a fourth in one year. Rapidly growing primary care private practice. Very pleasant, four day week, low bureaucracy office practice. Light call, housestaff coverage at excellent hospital. Many opportunities to teach medical students and residents. Mountains, skiing, and ocean about one hour away. Contact Laurie Thompson, (503) 222-1758, or send CV to Downtown Medical Associates, 511 SW 10th Ave, Ste 1114, Portland, OR 97205.

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NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

GYNECOLOGIST needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648; (405) 225-2511.

PEDIATRICIANS. FHP is one of the nation's largest and most progressive HMOs. At FHP, physicians can enjoy a secure practice and outstanding benefits without the complications of private practice. We currently have excellent opportunities at our medical centers in Albuquerque for skilled Pediatricians. Must be BC/BE. Previous experience preferred. Additional opportunities available in Arizona, California, Guam, and Utah. Please call Kathleen Orwat at (505) 881-7900 or (800) 444-4347 or send your CV to FHP, Professional Staffing Dept, 4300 San Mateo NE, Albuquerque, NM 87110. Equal Opportunity Employer.

SOUTHERN CALIFORNIA

Dynamic, multispecialty group is seeking specialists and Primary Care Physicians for our facilities in Los Angeles and Orange Counties. Excellent compensation and benefit package. Please send CV to:

Director/Professional Recruitment
CIGNA Healthplans of CA
505 N. Brand Blvd, #400-49
Glendale, CA 91203

PHYSICIANS WANTED

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

INTERNAL MEDICINE, SEATTLE. BE/BC full-time Primary Care, to join two other Internists now. Well established growing progressive practice near major north end hospital. Income guarantee first two years. CV to Internal Medicine, 540-C NE Northgate Way, Ste 139, Seattle, WA 98125.

OCCUPATIONAL MEDICINE. MD, BE/BC with Toxicology experience to join established free-standing clinic. Attractive opportunity for growth. Competitive salary and benefits. Send CV to Manager, MBI Industrial Medicine, Inc, 2539 N. 35th Ave, Phoenix, AZ 85009.

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

GENERAL INTERNIST. Group practice located in beautiful northern California wine country seeks General Internist. We are opening a new 106-bed hospital February 1990; a superb opportunity to join a growing, thriving practice. Excellent salary, benefits, security, and ample time off. Please send CVs to Richard Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

FAMILY PRACTITIONERS AND GENERAL INTERNISTS, Sacramento Kaiser Permanente. Must be BC/BE. Family Practitioners join 23 Family Practitioners with excellent consultant support. Internists work in established Department of Medicine, experience continuing growth. Pleasant practice setting where physicians are free to provide the highest quality medicine with full access to diagnostic and therapeutic services. Affiliated with University of California, Davis, providing a substantial part of their residency programs. Excellent financial package includes in-house CME and retirement package, with no billing or practice management headaches. To join our successful, growing medical group, Family Practitioners send CV to Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825. Internists send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

(Continued on Page 243)

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PHYSICIANS WANTED

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

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Urgent Care
Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

CALIFORNIA, SAN FRANCISCO BAY AREA. Saint Louise Health Center is a new hospital scheduled to start operations October 1. This is an exciting opportunity for BC/BE Emergency Physicians to organize and start-up a level II emergency service. Located in Morgan Hill, a high growth desirable residential area on the outer fringe of Silicon Valley, this position includes membership in a prestigious northern California staffing group which is democratically governed and academically oriented. Please mail CV to Kate Lawlor, Emergency Physicians' Medical Group, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

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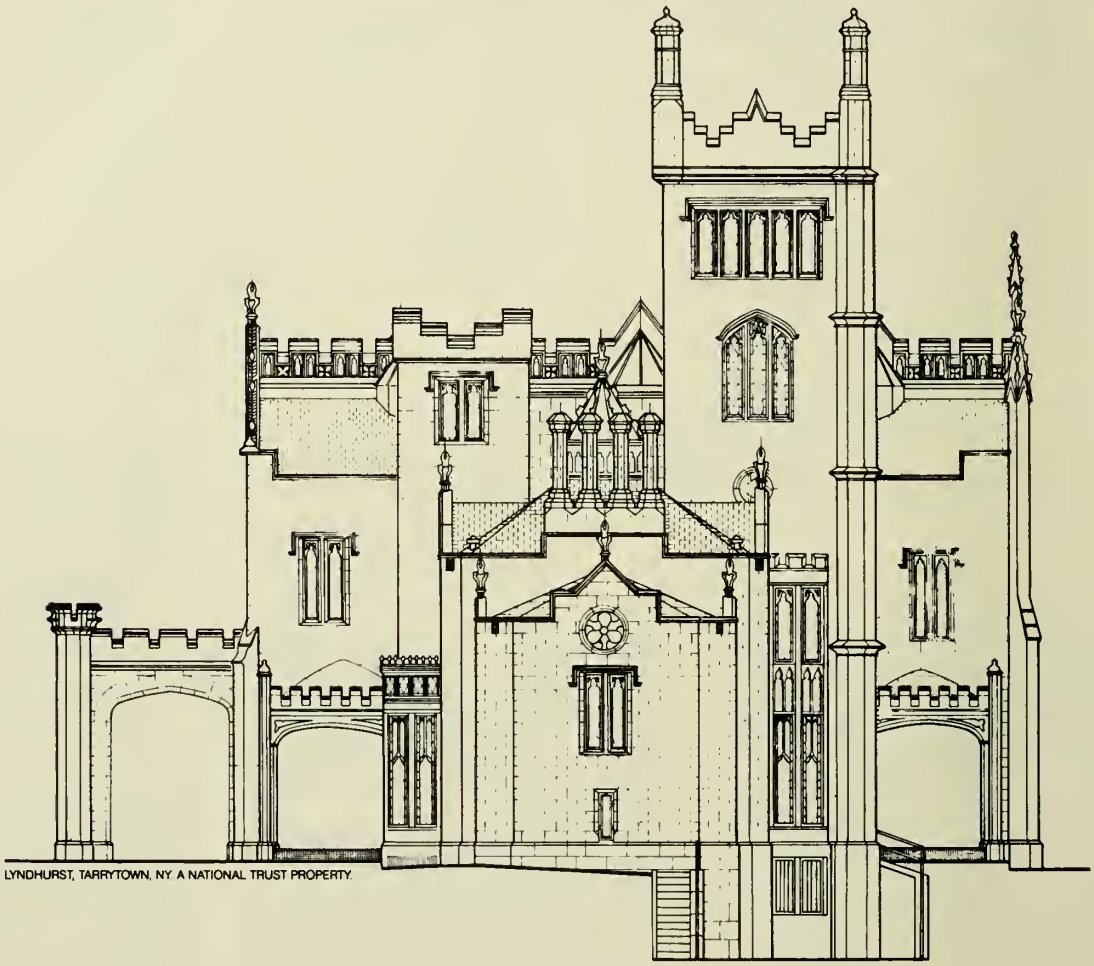

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NATIONAL SYMPOSIUM ON
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October 14, 1989

Kern Medical Center, California State University, Bakersfield, and Kern County Health Department will hold a symposium on "Molecular Epidemiology—A New Tool in Investigating Childhood Cancer Clusters," at Dore Theater, CSUB. Specific topics will include:

- Monitoring Human Exposure of Carcinogenesis and Mitogenic Agents
- Biologic Markers in Environmental Epidemiology
- Genetic Testing and Chromosomal Studies in Childhood Cancer
- Genetic Screening and Monitoring High-Risk Populations

Members of the medical and scientific community, governments and industry are invited to participate.

For further information, contact:

Sheldon Freedman, MD
Symposium Chairman
Kern Medical Center
1830 Flower St
Bakersfield, CA 93305
(805) 326-2256

(Symposium Co-Chairmen: Paul Dhariwal, MD, and Hans Einstein, MD)

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MEETINGS

KAUAI, HAWAII, JANUARY 20-28, 1990
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Family Practice: Caring and Curing, January 20-25. Pain Management: Compleat Approach, January 26-28. Contact **Academy for Continuing Education of Kauai, PO Box 457, Kalaheo, HI 96741.**

ST PAUL'S HOSPITAL CME COURSE, Vancouver, November 1, 2, 3, 1989. The 35th Annual St Paul's Hospital Continuing Medical Education Course will be held at the Vancouver Convention Centre. This popular course is directed to Family Physicians in both rural and urban practices and will provide excellent speakers on Back Pain; Hyperlipidemia; Emergency; Therapeutics; AIDS; Eyes/ENT. For further information: Susan Tate-Smith, Medical Services, St Paul's Hospital, 1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada; (604) 682-2344, loc 2721.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1990, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-29, 1989, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1990, date and location to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1990, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 13-15, 1989, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 28-October 1, 1989, SEATAC Red Lion, Seattle.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1990, date and location to be announced.

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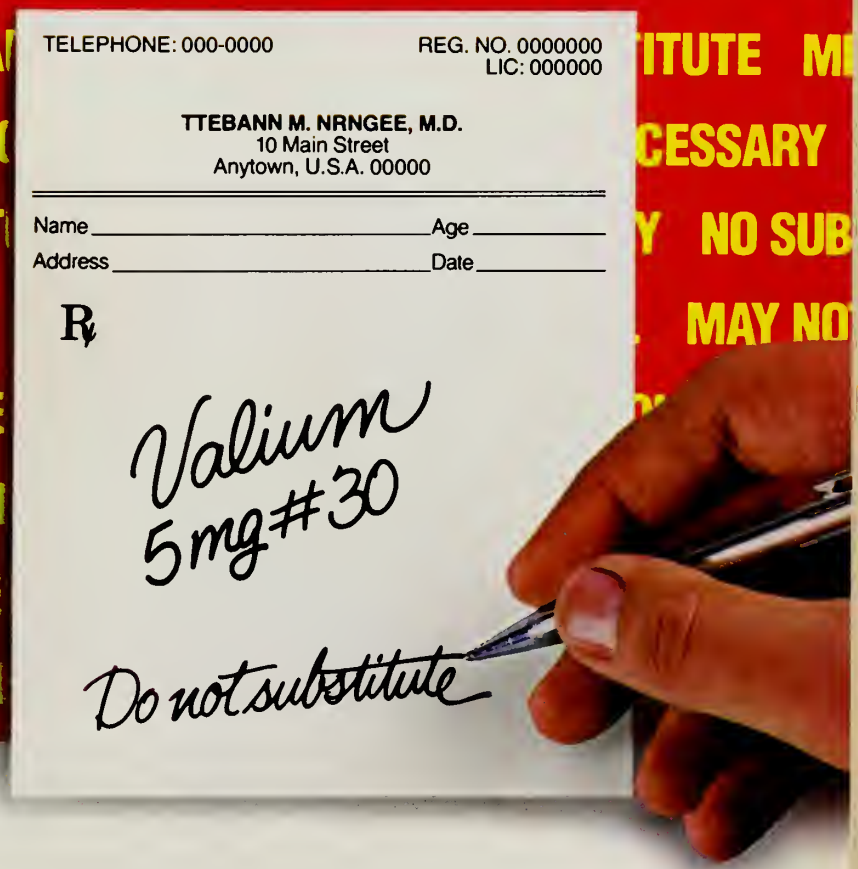

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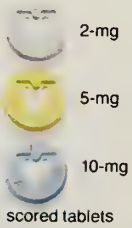

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*The antihypertensive effect may diminish at the end of the dosing interval.

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INDICATIONS AND USAGE. ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **DRUG INTERACTIONS. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL. **Agents Increasing Serum Potassium:** ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Lithium:** Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. **Human Experience:** There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use the ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward

support of blood pressure and renal perfusion with the administration of fluids and pressores as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below

Percent of Patients in Controlled Studies

	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia. (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response.

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A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: ***General.*** Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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SEARLE

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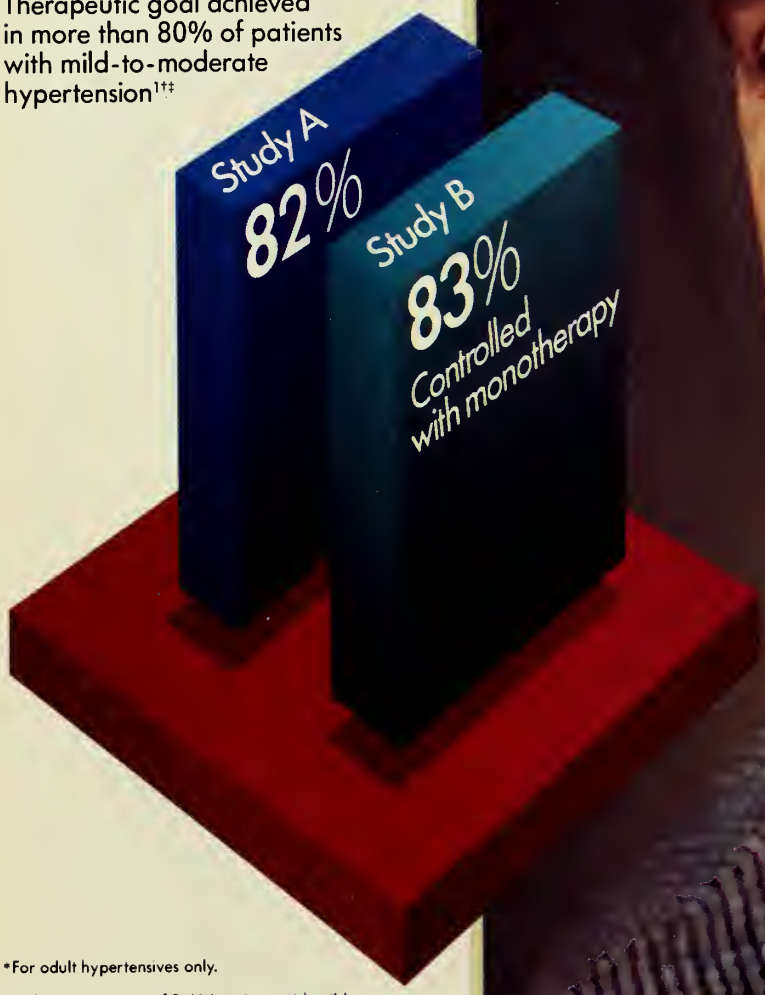
Therapeutic goal achieved in more than 80% of patients with mild-to-moderate hypertension[1†‡]



*For adult hypertensives only.

†Eighty-two percent of 3,604 patients with mild-to-moderate hypertension (30–70 years) achieved goal blood pressure (DBP ≤90 mm Hg) in an open, multicenter, six-week study.

‡In a double-blind, forced dose titration comparative study of 394 black patients with mild-to-moderate hypertension (18–70 years), 83% of those randomized to Calan SR (n=54) at a dosage of 360 mg/day achieved goal blood pressure (DBP<90 mm Hg or >10 mm Hg reduction).

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ONCE-A-DAY
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Verapamil HCl 240mg
SUSTAINED-RELEASE CAPLETS

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence. 5/9/88 • C88-W5282V-1

References: 1. Data on file, G.D. Searle & Co. 2. Baird MG, Bentley-Taylor MM, Carruthers SG, et al: A study of efficacy, tolerance and compliance of once-daily versus twice-daily metoprolol (Betaloc®) in hypertension. *Clin Invest Med* 1984;7:95–102. 3. Fletcher AE, Chester PC, Hawkins CMA, et al: The effects of verapamil and propranolol on quality of life in hypertension. *J Hum Hypertens* 1989;3:125-130.

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
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3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
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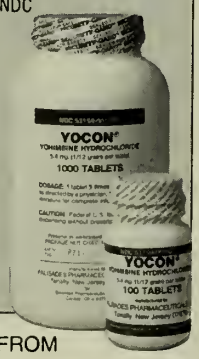

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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Indonesian Study Trip

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Batik painting by Wiji Hartono/Kabul, Yogyakarta, Indonesia

2nd Annual University of Minnesota Primary Care Update to Bali and Yogyakarta

Educational Program

The 1990 program will focus on emergency medicine, cardiovascular disease, and obstetrics and gynecology. Faculty will be from the University of Minnesota Medical School. In addition presentations and demonstrations will be given by Indonesian physicians and healers, and we will tour a general hospital in Bali. The Yogyakarta extension includes a visit to a community clinic and to a private Moslem hospital.

Indonesia

In addition to its beautiful beaches, Bali's attractions include its fascinating Hindu culture, volcanic mountains, terraced rice paddies, busy markets, and many craft shops. Yogyakarta, long the arts center of Indonesia, is an excellent example of the eclectic Moslem culture of Central Java.

Bali Tour Includes

• Roundtrip airfare from Los Angeles to Bali via Garuda Indonesia Airlines • Seven nights accommodation at the Sanur Beach Hotel, Bali • American breakfast daily, welcome and farewell dinners • Two half-day tours: Besakih Temple, Tanah Lot, Monkey Forest, Ubud, and Mas • Roundtrip transfers • Porterage and hospitality desk at the Sanur Beach Hotel

Optional Extension to Yogyakarta (2/25-28)

• Roundtrip airfare from Bali • Three nights accommodation at the Puri Artha Cottages • City tour • Visit to Borobudur, largest Buddhist temple in the world • Clinic and hospital visits • Optional dinner at Sultan's Palace

Cost Summary

Total land and air from Los Angeles (per person, double occupancy) $1595
Yogyakarta extension (per person, double occupancy) $ 215

For Further Information

Office of Continuing Medical Education, Continuing Education and Extension, Box 202, UMHC, 420 Delaware St. S.E., Minneapolis, MN 55455; telephone 612-626-5525; FAX 612-626-4411. Bart Galle, PhD, Director, 612-626-4046 • Group Travel Directors: outside Minnesota 1-800-222-7907; Telex 4950462; FAX 612-881-6276

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 1, 8, 15, 29—**Medical Service Grand Rounds.** Carl T. Hayden VA Medical Center, Phoenix. Fridays. Contact: Dr Felicetta, (602) 255-5551, Ext 6436.

September 5, 12, 19, 26—**GI Grand Rounds.** Carl T. Hayden VA Medical Center, Phoenix. Wednesdays. Contact: Dr Sanowski, (602) 255-5551, Ext 7618.

September 12—**Depression in the Elderly.** Holy Cross Hospital, Nogales. Tues. Contact: Judy Doan, (602) 287-4722.

September 13-April 11—**Cochise County Medical Society CME Mini Series.** Monthly. Contact: Continuing Medical Education, (602) 626-7832.

September 21—**Geriatric Grand Rounds—Kenneth Brummel-Smith, MD.** St Mary's Hospital, Tucson. Thurs. Contact: Gail Kreshner Riggs, (602) 626-6854.

September 22-23—**Cancer Reviews.** Orangetree Golf Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

September 28—**Family Systems (in Alcohol and Chemical Dependency).** Benson Hospital, Benson. Thurs. Contact: Judy Doan, (602) 287-4722.

October 13-14—**Diabetic Complications in the Elderly and Geriatric Assessment.** Walter O. Boswell Memorial Hospital, Sun City. Contact: A. R. Colwell, MD, (602) 974-4448.

October 19-20—**Far West Image Perception Conference.** Westward Look Resort, Tucson. Thurs-Fri. Contact: U of A, CME, (602) 626-7832.

October 27-28—**Therapeutics Update.** Poco Diablo Resort, Sedona. Fri-Sat. Contact: U of A, CME, (602) 626-7832.

November 3—**Infectious Disease Update.** Arizona Health Sciences Center, Tucson. Fri. Contact: U of A, CME, (602) 626-7832.

November 3-4—**Neuro-oncology and Stereotactics: Current Approaches to CNS Neoplasia.** Hyatt Gainey Ranch Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 4—**Practice for an Aging Population: What Will It Be Like in the 1990s.** Sonora Desert Hospital, Tucson. Sat. Contact: Gail Kershner Riggs, (602) 626-6854.

November 9-11—**Second Annual Spine Workshop.** Camelback Inn, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix 85013.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

November 10-11—**9th Annual Southwestern Poison Symposium.** Doubletree Hotel, Tucson. Fri-Sat. Contact: Arizona Poison Control Center, (602) 626-6016.

November 18—**Techniques in Gynecologic Surgery: Slide and Video Conference.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Mon. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

December 1-2—**External Rhinoplasty Course.** Tucson. Fri-Sat. Contact: Ruth Ann Lynn, (602) 626-7764.

December 2-3—**Arizona Chapter, American College of Surgeons.** Westward Look Resort, Tucson. Sat-Sun. Contact: U of A, CME, (602) 626-7832.

December 13—**Dean's Education Rounds.** Arizona Health Sciences Center, Tucson. Wed. Contact: Jack Roberts, (602) 626-4555.

December 14—**Genetics Update.** Flagstaff Medical Center, Flagstaff. Thurs. Contact: H. Eugene Hoyme, MD, (602) 795-5675 (Tucson) or William Austin, MD, (602) 774-1811 (Flagstaff).

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 21-22—**Modern Approaches to Allergy and Clinical Immunology.** UCSF at Hyatt Union Square, San Francisco. Thurs-Fri. 15 hrs. $300. Contact: UCSF.

September 23—**Advances in Allergy and Infectious Diseases.** Alexian Brothers Hospital at Red Lion Inn, San Jose. Sat. 8 hrs. $25. Contact: Alexian Brothers Hospital, 225 N Jackson Ave, San Jose 95116. (408) 259-5000.

ANESTHESIOLOGY

September 22-24—**Anesthesia Practice 1989.** Anesthesiology Educational Foundation at Hyatt Regency, Monterey. Fri-Sun. 12.5 hrs. Contact: AEF, PO Box 24230, Los Angeles 90024. (213) 825-0736.

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. 15 hrs. Contact: UCD.

January 11-14—**Anesthesia Update 1990.** UCSD at Hotel Del Coronado, Coronado. Thurs-Sun. Contact: UCSD.

(Continued on Page 267)

In Memoriam

Arizona Medical Association

BARRATT, GEORGE E., Yuma. Died May 12, 1989, aged 37. Graduate of Loyola University of Chicago Stritch School of Medicine, 1980. Licensed in Arizona in 1980. Dr Barratt was a member of the Yuma County Medical Society.

TRAHERN, CHARLES A., Prescott. Died Jun 9, 1989, aged 67. Graduate of University of Louisville School of Medicine, 1951. Licensed in Arizona in 1973. Dr Trahern was a member of the Yavapai County Medical Society.

California Medical Association

ALEXANDER, ALEXANDER, Los Angeles. Died Apr 1, 1989, aged 57. Graduate of Cervenko Higher Institute of Medicine, 1956. Licensed in California in 1974. Dr Alexander was a member of the Los Angeles County Medical Association.

ARCELLANA, VINCENTE A., Fairfield. Died Jun 12, 1989, aged 36. Graduate of University of California, San Francisco, 1979. Licensed in California in 1987. Dr Arcellana was a member of the Napa County Medical Society.

AXTELL, GLENN A., Oakland. Died Jun 14, 1989, aged 79. Graduate of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Axtell was a member of the Alameda-Contra Costa Medical Association.

BARTH, TUCKER A., Stockton. Died Jul 22, 1989. Graduate of University of Colorado School of Medicine, Denver, 1946. Licensed in California in 1957. Dr Barth was a member of the San Joaquin County Medical Society.

BECKER, ROBERT. Died May 9, 1989, aged 64. Graduate of Loma Linda University School of Medicine, 1957. Licensed in California in 1958. Dr Becker was a member of the Los Angeles County Medical Association.

BISSELL, DWIGHT M., Saratoga. Died Apr 15, 1989, aged 86. Graduate of Stanford University School of Medicine, 1936. Licensed in California in 1936. Dr Bissell was a member of the Santa Cruz County Medical Society.

BORGNINO, FRANCIS C., Berkeley. Died May 18, 1989, aged 72. Graduate of McGill University Faculty of Medicine, Montreal, 1945. Licensed in California in 1946. Dr Borgnino was a member of the Alameda-Contra Costa Medical Association.

BROCK, FRED C. Died Apr 14, 1989, aged 91. Graduate of Med Fak Der Johann Wolfgang Goethe University, 1922. Licensed in California in 1940. Dr Brock was a member of the Los Angeles County Medical Association.

CHRISTENSON, ERNEST CHARLES, Deer Park. Died Jun 17, 1989, aged 76. Graduate of Loma Linda University, 1941. Licensed in California in 1943. Dr Christenson was a member of the Napa County Medical Society.

CRANDALL, JOHN I., San Leandro. Died Jun 27, 1989, aged 68. Graduate of University of Colorado School of Medicine, Denver, 1959. Licensed in California in 1964. Dr Crandall was a member of the Alameda-Contra Costa Medical Association.

DHARNIDHARKA, SAJJAN G., Stockton. Died May 26, 1989, aged 44. Graduate of University of Bombay Affiliated Medical Colleges, 1967. Licensed in California in 1975. Dr Dharnidharka was a member of the San Joaquin County Medical Society.

DRIVER, MAYNARD D., Berkeley. Died Jan 11, 1989, aged 57. Graduate of Howard University College of Medicine, Washington, DC, 1961. Licensed in California in 1963. Dr Driver was a member of the Alameda-Contra Costa Medical Association.

DUNSCOMBE, COLBY W., Lodi. Died Jun 27, 1989, aged 76. Graduate of Loma Linda University School of Medicine, 1938. Licensed in California in 1938. Dr Dunscombe was a member of the San Joaquin County Medical Society.

DUPREY, WILLIAM, Fresno. Died Jun 18, 1989, aged 61. Graduate of St Louis University School of Medicine, 1954. Licensed in California in 1959. Dr Duprey was a member of the Fresno-Madera Medical Society.

EDWARDS, EDWARD. Died Mar 17, 1989, aged 59. Graduate of Washington University School of Medicine, St Louis, 1955. Licensed in California in 1959. Dr Edwards was a member of the Los Angeles County Medical Association.

GLOVER, CHARLES B., Danville. Died Apr 9, 1989, aged 51. Graduate of Louisiana State University School of Medicine, 1963. Licensed in California in 1965. Dr Glover was a member of the Alameda-Contra Costa Medical Association.

GORDON, ARNOLD. Died Mar 25, 1989, aged 76. Graduate of Rush Medical College, Chicago, 1937. Licensed in California in 1938. Dr Gordon was a member of the Los Angeles County Medical Association.

GRAHAM, VINCENT P., Capitola. Died Feb 1989, aged 76. Graduate of Harvard Medical College, Boston, 1938. Licensed in California in 1946. Dr Graham was a member of the Santa Cruz County Medical Society.

HILLENBRAND, CARL M., San Diego. Died Jun 6, 1989, aged 79. Graduate of Albany Medical College, Albany, New York, 1935. Licensed in California in 1947. Dr Hillenbrand was a member of the San Diego County Medical Society.

HILLS, OSCAR W., San Mateo. Died Jul 12, 1989, aged 72. Graduate of Harvard Medical School, Boston. Licensed in California in 1952. Dr Hills was a member of the San Mateo County Medical Society.

HUNTINGTON, ROBERT, Bakersfield. Died Jul 14, 1989, aged 82. Graduate of Yale Medical School, New Haven, Connecticut, 1933. Licensed in California in 1946. Dr Huntington was a member of the Kern County Medical Society.

MORTON, PAUL H., Coronado. Died May 23, 1989, aged 78. Graduate of Jefferson Medical School, Philadelphia, 1938. Licensed in California in 1939. Dr Morton was a member of the San Diego County Medical Society.

ROBBINS, WILFRED T., Santa Barbara. Died Jun 9, 1989, aged 77. Graduate of University of California, San Francisco, 1939. Licensed in California in 1939. Dr Robbins was a member of the Santa Barbara County Medical Society.

SAVITZ, SAUL. Died May 14, 1989, aged 83. Graduate of Temple University School of Medicine, Philadelphia, 1930. Licensed in California in 1944. Dr Savitz was a member of the Los Angeles County Medical Association.

STRATTON, MICHAEL L. Died Apr 24, 1989, aged 44. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1970. Licensed in California in 1971. Dr Stratton was a member of the Los Angeles County Medical Association.

SUMMERS, BRUCE M., Riverside. Died May 25, 1989, aged 93. Graduate of Indiana University School of Medicine, Indianapolis, 1923. Licensed in California in 1953. Dr Summers was a member of the Riverside County Medical Association.

TODD, V. STANLEY. Died Feb 2, 1989, aged 79. Graduate of University of Iowa College of Medicine, Iowa City, 1936. Licensed in California in 1946. Dr Todd was a member of the Stanislaus Medical Society.

WALTERS, STEPHEN, San Francisco. Died Feb 2, 1989, aged 43. Dr Walters was a member of the San Francisco Medical Society.

WEST, R. KIRBY, Oakland. Died Jul 2, 1989, aged 68. Graduate of University of Rochester, New York, 1948. Licensed in California in 1949. Dr West was a member of the Alameda-Contra Costa Medical Association.

WETMORE, CLYDE T. Died May 11, 1989, aged 103. Graduate of Stanford University, 1915. Licensed in California in 1920. Dr Wetmore was a member of the Alameda-Contra Costa Medical Association.

WHITELY, JAMES S., South Lake Tahoe. Died Mar 19, 1989, aged 66. Graduate of Stanford University, 1954. Licensed in California in 1955. Dr Whitely was a member of the Sacramento-El Dorado Medical Society.

WILSON, WILLIAM J. Died Feb 24, 1989, aged 57. Graduate of University of Missouri, 1958. Licensed in California in 1974. Dr Wilson was a member of the Los Angeles County Medical Association.

WOOLLEY, LEGRAND G., Monterey. Died May 4, 1989, aged 76. Graduate of Stanford University, 1944. Licensed in California in 1973. Dr Woolley was a member of the Monterey County Medical Society.

ZELLER, ROBERT F., Stockton. Died Jun 25, 1989, aged 77. Graduate of Loyola University of Chicago Stritch School of Medicine, 1940. Licensed in California in 1943. Dr Zeller was a member of the San Joaquin County Medical Society.

Utah Medical Association

ISGREEN, EMIL P., Salt Lake City. Died Jun 13, 1989, aged 79. Graduate of University of Utah, Salt Lake City, 1945. Licensed in Utah in 1951. Dr Isgreen was a member of the Salt Lake County Medical Society.

LLOYD, BRUCE A., Salt Lake City. Died Jun 22, 1989, aged 66. Graduate of University of Utah, Salt Lake City, 1951. Licensed in Utah in 1954. Dr Lloyd was a member of the Salt Lake County Medical Society.

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†See Warnings and Precautions.

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BRIEF SUMMARY
Professional Use Information

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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

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(Continued from Page 263)

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February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Sat. Contact: Murray G. Atnikov, MD, PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

CARDIOLOGY

September 20—**Optimum Use of Diagnostic and Therapeutic Technologies in Clinical Practice.** American Heart Association Los Angeles at Beverly Hilton. Wed. 9 hrs. $120. Contact: Marlin Ledbetter, 3550 Wilshire Blvd, Ste 500, Los Angeles 90010. (213) 385-4231.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
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(Continued on Page 272)

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VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy:* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium:* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium:* See WARNINGS, *Hydrochlorothiazide*; and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies of VASERETIC in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Enalapril Maleate: Post-marketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity, such as patent ductus arteriosus, have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk; however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Other adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Body as a Whole:* Syncope, chest pain, abdominal pain. *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia. *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Skin:* Pruritus, rash. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, decreased libido, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation; hypotension, angina pectoris. *Digestive:* Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, glossitis. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion, ataxia. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, pneumonia, bronchitis, rhinorrhea, asthma, upper respiratory infection. *Skin:* Herpes zoster, alopecia, flushing, photosensitivity. *Other:* Vasculitis, blurred vision, taste alteration. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide—Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 3418—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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For respiratory tract infections due to susceptible strains of indicated organisms.

Summary.
Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
Contraindication: Known allergy to cephalosporins.
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever): 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

[061088L]

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CONTINUING MEDICAL EDUCATION

(Continued from Page 267)

September 22-23—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Bally's Casino Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

September 22-24—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Le Meridien Hotel, San Diego. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

October 13-14—**Coronary Heart Disease Update.** Medical Education Resources at Sheraton Fisherman's Wharf, San Francisco. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

October 27-29—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Bally's Casino Hotel, Las Vegas, Nevada. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

November 3-4—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Rancho Las Palmas, Rancho Mirage. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

December 1-2—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 10-12—**Cardiovascular Disease in the Elderly.** UCI at Fess Parker's Red Lion Resort, Santa Barbara. Wed-Fri. Contact: UCI.

January 19-20—**Coronary Heart Disease Update.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

DERMATOLOGY

October 14-15—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF at Laurel Heights Campus. Sat-Sun. 10 hrs. $205. Contact: UCSF.

November 2-5—**International Hot Spots in Dermatology: The Patient, the Disease, the Physician and the Art.** Kauai Academy of Continuing Education at Stouffer's Waiohai Beach Resort, Poipu, Hawaii. Thurs-Sun. Contact: David J. Elpern, MD, PO Box 457, Kalaheo, HI 96741.

January 18-20—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande at Torrey Pines, La Jolla. Thurs-Sat. $400. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 19-21—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess. Fri-Sun. Contact: UCSD.

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. $415. Contact: UCD.

(Continued on Page 273)

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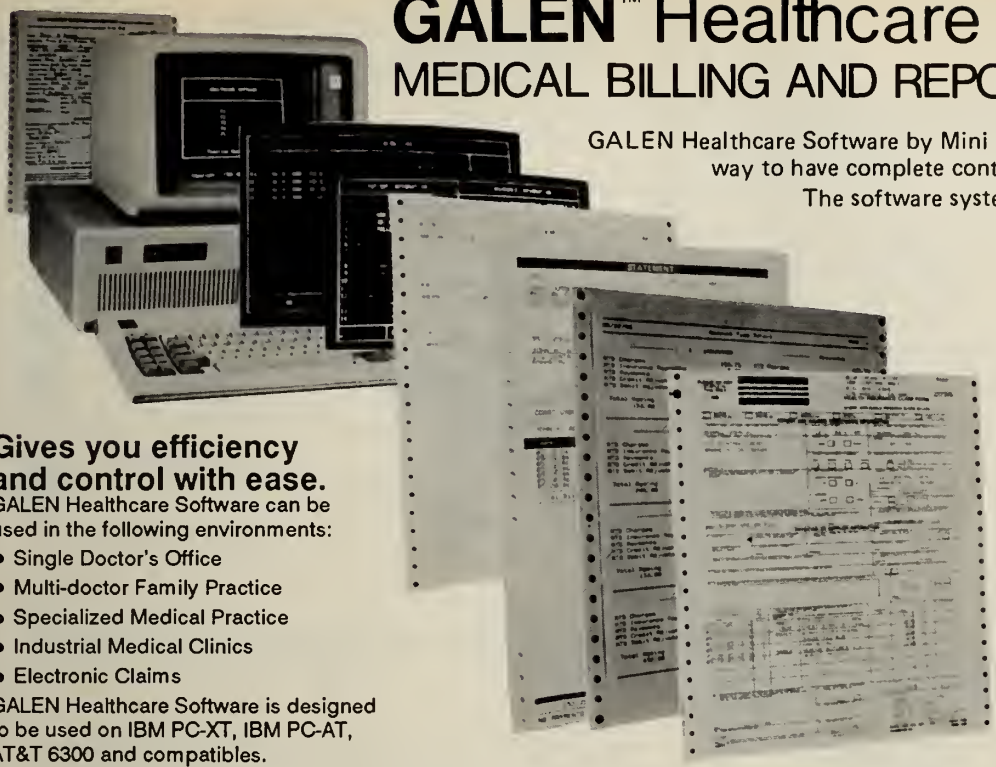

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CONTINUING MEDICAL EDUCATION

(Continued from Page 272)

December 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. $450. Contact: UCSD.

December 7-9—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 16 hrs. $220. Contact: UCSF.

December 11-15—**Emergency Medicine Symposium III.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

INTERNAL MEDICINE

September 24-26—**Advanced TMJ Arthroscopy.** UCSD. Sun-Mon. Contact: UCSD.

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. 16 hrs. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 18-21—**Advances in Gastroenterology.** UCSD at Hotel Del Coronado, San Diego. Thurs-Sun. 23 hrs. $425. Contact: UCSD.

January 19-20—**The Medical Dysphagia Team: From Intensive Care to Rehabilitation.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 2-3—**7th Annual Reider Laser-Urology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 9-10—**2nd Annual Bristol Myers Symposium on Neurosciences.** UCSD at Price Center, La Jolla. Fri-Sat. 12 hrs. $50. Contact: UCSD.

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 18-23—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

(Continued on Page 274)

CONTINUING MEDICAL EDUCATION

(Continued from Page 273)

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

October 12-13—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Newport Marriott Hotel, Newport Beach. Thurs-Fri. Contact: UCI.

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

January 28-February 1—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 2-3—**7th Annual Reider Laser-Gynecology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

OPHTHALMOLOGY

September 15-16—**Uveitis Frontiers: Diagnostic, Medical and Surgical Approaches to Uveitis.** UCSF at Quail Lodge, Carmel Valley. Fri-Sat. Contact: UCSF.

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

PEDIATRICS

October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 3-5—**Current Advances in Pediatrics.** American Academy of Pediatrics California Chapter 4 at Disneyland Emerald Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: California Chapter 4, AAP, PO Box 1297, Orange 92668. (714) 978-2415.

November 4—**Pediatric Protein Metabolism.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 12-13—**North American Society for Pediatric and Adolescent Gynecology** at Red Lion Hotel, Costa Mesa. Fri-Sat. Contact: UCI.

January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

February 2-4—**Current Concepts in Pediatric Medicine 1990.** Children's Hospital at Hyatt Islandia, San Diego. Fri-Sun. Contact: Children's Hospital and Health Center, Medical Education Dept, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

(Continued on Page 276)

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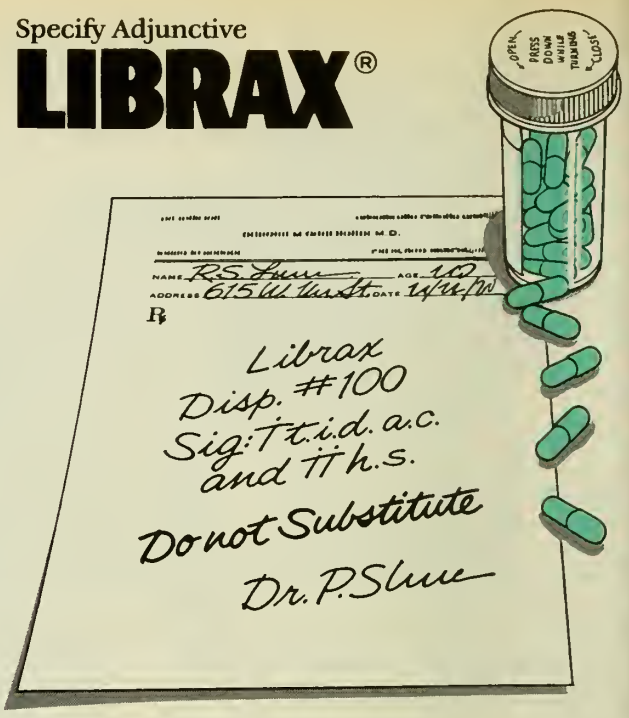

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

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Please see summary of prescribing information on adjacent page.

CONTINUING MEDICAL EDUCATION

(Continued from Page 274)

PSYCHIATRY

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

October 26-29—**Psychosomatic Medicine and Consultation-Liaison Psychiatry in a High-Technology World.** Academy of Psychosomatic Medicine at Riviera Hotel, Las Vegas, Nevada. Thurs-Sun. Contact: Academy of Psychosomatic Medicine, 5824 N Magnolia, Chicago, IL 60660. (312) 784-2025.

October 1989-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

RADIOLOGY

September 23-24—**Weekend MRI Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Sat-Sun. 12 hrs. $195. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

October 2-5—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center and University of Cincinnati College of Medicine at Ritz-Carlton Hotel, Laguna Niguel. Mon-Thurs. 18 hrs. $395. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 7-8—**Ultrasound Update: 1989.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. Contact: UCD.

October 12-14—**Update in Pediatric Imaging for the Practicing Radiologist.** Children's Hospital Medical Center Cincinnati at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sat. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 10-12 & January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

December 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 60009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 1-4—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 16 hrs. $375. Contact: UCSD.

SURGERY

September-December—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

September 15—**Ultrasonic Liver Surgery.** UCD at University Club, Davis. Fri. 8 hrs. $250. Contact: UCD.

September 22-24—**Frontiers in Solid Organ Transplantation.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sun. $125. Contact: UCLA.

September-June—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 38 hrs. $1125. Contact: UCSD.

October 11-14—**Hip and Knee Reconstructive Surgery 1989.** UCLA at Sheraton Kauai Hotel Poipu Beach, Kauai, Hawaii. Wed-Sat. Contact: UCLA. (213) 825-5840.

November 13-15—**21st Annual Surgical Congress.** Orange County Surgical Society at Le Meridien Hotel, Newport Beach. Mon-Wed. 16 hrs. Contact: OCSS, PO Box 1297, Orange 92666. (714) 978-3983.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

January 22-26—**13th Annual Assembly in Surgery.** UCSD at Catamaran Resort Hotel. Mon-Fri. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

September 23—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Scripps Amphitheater. Sat. 6 hrs. $50. Contact: Bonny Mower, 10666 N Torrey Pines Rd, Box 400S, La Jolla 92037. (619) 554-8556.

October 7—**Selected Topics in Diabetes Mellitus.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 5 hrs. $25. Contact: UCLA.

October 9-13—**Selected Topics in Sports Medicine in Conjunction With the Ironman Triathlon World Championship.** Tropical Seminars at Kona Surf Resort, Kailua-Kona, Hawaii. Contact: Robert Bethel, DO, PO Box 1399, Poulsbo, WA 98370. (206) 697-5776.

October 12-14—**Medicine Today.** UCSD at Mandeville Auditorium. Thurs-Sat. Contact: UCSD.

October 13-15—**Medical Office Laboratory Second Annual Conference.** San Diego State University at Mission Valley Marriott Hotel. Fri-Sun. 17 hrs. Contact: SDSU, College of Extended Studies, Certificate Program, San Diego, CA 92182. (619) 594-6255.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 21—**9th Annual Norman Sharrer Symposium: Common Difficult Treatment Syndromes.** Kaweah Delta District Hospital at Holiday Inn, Visalia. Sat. 6 hrs. $25. Contact: Kaweah Hospital, 400 W Mineral King Ave, Visalia 93291. (209) 625-7308.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 2-4—**The Challenge of Diabetes.** Annenberg Center for Health Sciences at Eisenhower at Rancho Mirage. Thurs-Sat. 15 hrs. Contact: Registration Secretary, (800) 321-3690.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 6-9—**Primary Care Update: 74th Scientific Assembly.** Interstate Postgraduate Medical Association at Town & Country Hotel, San Diego. Mon-Thurs. 24 hrs. $200. Contact: IPMA, PO Box 5474, Madison, WI 53705. (608) 257-1401.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas Hilton. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

(Continued on Page 277)

(Continued from Page 276)

December 2—**7th Annual Reider Laser Center International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers With ND: YAG Laser Workshop.** UCI at Center for Health Education, Long Beach. Contact: UCI.

December 6—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda at Los Angeles. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 891-2473.

December 9-10—**Travel Medicine '89.** American Society of Tropical Medicine and Hygiene at Honolulu, Hawaii. Sat-Sun. 12 hrs. $250. Contact: Linda Limauro, 20 York St, New Haven, CT 06504. (203) 785-2476.

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 20—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $110. Contact: Kim I. Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

January 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Kona Surf Resort, Kona, Hawaii. 1 week. 21 hrs. $395. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

January 27-28—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Holiday Inn Union Square, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

February 1-3—**13th Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Mon-Fri. Contact: UCSD.

February 7-9—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 21 hrs. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 9-10—**Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 22 hrs. $350. Contact: UCSD.

IDAHO

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** University of Washington at Sun Valley. Fri-Sun. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 441-9762.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 15-16—**Essentials of Health Care for the Elderly.** University of New Mexico Conference Center, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

September 15-16—**New Mexico Chapter, American College of Surgeons—Scientific Meeting.** Marriott Hotel, Albuquerque. Contact: Jorge A. Wernly, MD, Surgery Dept, Univ of New Mexico Hospital, 2211 Lomas Blvd, NE, Albuquerque 87131. (505) 277-6901.

September 16-17—**The Special Senses in Pediatrics: Evaluation of Eye, Ear, Nose, and Throat Problems.** Holiday Inn, Gallup. Contact: Robert Greenburg, MD, New Mexico Pediatric Society, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431.

September 17-20—**Prevention and Treatment: The Family—Second Annual Southwest Regional Substance Abuse Conference.** Doubletree Hotel and Convention Center, Albuquerque. Contact: Marian Greher, 1479 Morning Glory NE, Albuquerque 87122. (505) 298-1630.

September 22-23—**Southwestern Psychiatric Symposium on Schizophrenia and Depression.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

October 12-14—**Management of Radiation Accidents.** Sheraton Old Town, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, (505) 277-3942.

November 18—**Affective Disorders.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

January 20—**Neuropsychiatry.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

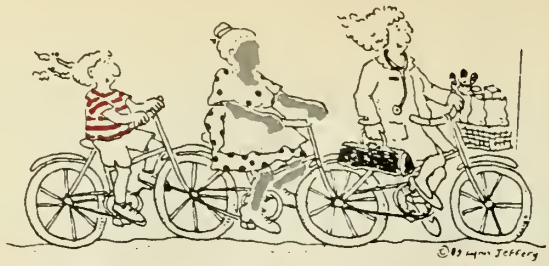
MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 21-23—**Utah Perinatal Association** (Sponsor: UUMC). Thurs-Sat. University Park Hotel, Salt Lake City. Contact: Raine Beach, (801) 581-2598.

(Continued on Page 278)



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American Medical Women's Association
74th Annual Meeting, October 25-29, 1989
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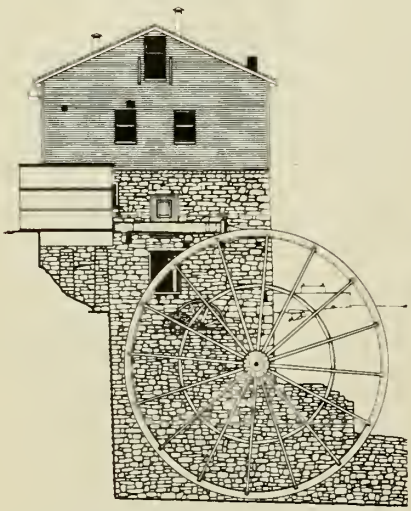

Write:
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1785 Massachusetts Ave., N.W.
Washington, D.C. 20036

CONTINUING MEDICAL EDUCATION

(Continued from Page 277)

September 28-29—**Laser Surgery: General Surgery ND: YAG, CO** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

October 12-13—**Laser Surgery: Gastroenterology ND: YAG** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 280)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 278)

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 15—**Exercise Physiology and Sports.** Walla Walla. Fri. Contact: St Mary Medical Center, (509) 525-3320.

September 15-16—**Allergy Update.** Seattle. Fri-Sat. Contact: U/W.

September 15-16—**Urology Update.** Seattle. Fri-Sat. Contact: VMMC.

September 16—**AIDS Issues.** Seattle. Sat. Contact: Evergreen Hospital, (206) 823-7599.

September 19—**Paranasal Sinus Disease.** Seattle. Tues. Contact: NW Hospital, (206) 368-1623.

September 20—**AIDS Conference.** Everett. Wed. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 22—**Ventilator Care.** Walla Walla. Fri. Contact: St Mary Medical Center, (509) 525-3320.

September 23—**AIDS Training for Washington State Professionals.** Seattle. Sat. Contact: WEAPA, (206) 448-4326.

September 29—**ACLS—Selected Issues.** Walla Walla. Fri. Contact: St Mary Medical Center, (509) 525-3320.

September 29—**Neurology Update.** Tacoma. Fri. Contact: CME Pierce County.

September 29—**Ophthalmology Scientific Session—WSMA Annual Meeting.** Seattle. Fri. Contact: WSMA.

October 6—**Cardiology Conference.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

October 6—**Current Issues in Nutrition Support.** Bellevue. Fri. Contact: (206) 764-2043 or (206) 548-6352.

October 11-12—**Common Office Problems.** Tacoma. Wed-Thurs. Contact: CME Pierce County.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

October 12-14—**Internal Medicine Review.** Seattle. Thurs-Sat. Contact: U/W.

October 18—**Nutrition.** Seattle. Wed. Contact: NW Hospital, (206) 368-1623.

October 19-21—**Washington State Academy of Physician Assistants Annual Fall Meeting.** Seattle. Thurs-Sat. Contact: VMMC.

October 27-28—**Sinus Surgery.** Seattle. Fri-Sat. Contact: U/W.

October 27-28—**Acid-Peptic Disease: New Perspectives.** Seattle. Fri-Sat. Contact: VMMC.

November 3—**The Injured Knee: Diagnosis, Treatment, and Therapy.** Seattle. Fri. Contact: VMMC.

November 3-4—**Medical Updates—School of Medicine.** Seattle. Fri-Sat. Contact: U/W.

November 10—**Sexual Abuse in Medical Practice.** Location to be announced. Fri. Contact: U/W.

November 10—**Outpatient Treatment of Infections: Oral Antibiotic Therapy.** Seattle. Fri. Contact: VMMC.

November 15—**Infectious Diseases.** Seattle. Wed. Contact: NW Hospital, (206) 368-1623.

November 16-17—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 17—**ENT/Ophthalmology.** Tacoma. Fri. Contact: PCMS, (206) 627-7317.

November 17—**23rd Annual Cancer Conference. Innovative Management of Cancer Patients.** Seattle. Fri. Contact: VMMC.

November 29-December 1—**Update on Surgery.** Seattle. Wed-Fri. Contact: U/W.

December 2—**AIDS Issues.** Seattle. Sat. Contact: Evergreen Hospital, (206) 823-7599.

December 6-10—**5th Annual Infectious Disease Conference.** Seattle. Wed-Sun. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 7-8—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

December 8—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** Sun Valley. Fri-Sun. Contact: U/W.

December 9-10—**The Anesthesiologists' Environment.** Seattle. Sat-Sun. Contact: WSSA, (206) 441-6020.

January 18—**Law & Medicine Symposium.** Tacoma. Thurs. Contact: PCMS, (206) 627-7137.

February 2—**Peripheral Vascular Disease, 1990.** Seattle. Fri. Contact: VMMC.

February 8-9—**Cancer Review 1990.** Tacoma. Thurs-Fri. Contact: PCMS, (206) 627-7137.

February 8-10—**Ophthalmology: Annual President's Meeting.** Seattle. Thurs-Sat. Contact: (206) 441-9762.

February 9-10—**Cardiology Conference.** Seattle. Fri-Sat. Contact: VMMC.

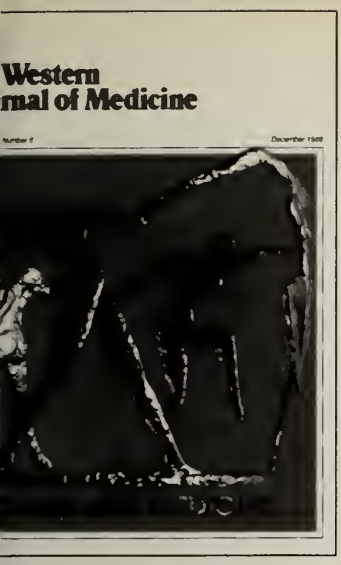
February 28—**AIDS Update.** Tacoma. Wed. Contact: PCMS, (206) 627-7137.

WYOMING

October 6—**Update on Infectious Diseases.** West Park Hospital, Cody. Fri. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody 82414. (307) 527-7501, ext 250.

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526. ◆

PECIAL ISSUES



Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

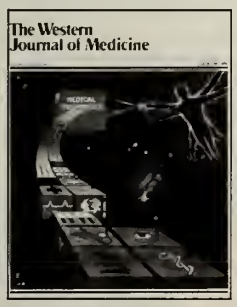
Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

S— lobal pective

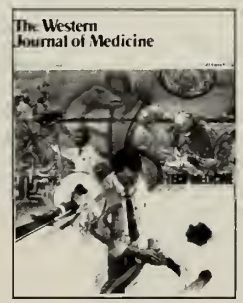
is issue, from ne World Health ization, con- the methods nitations of case reporting IV serologic s, summarizes of transmis- lefines geo- c patterns of , and examines idemiology of fections by con- Jonathan M. MD, Special Editor, 1987.

Medical Informatics



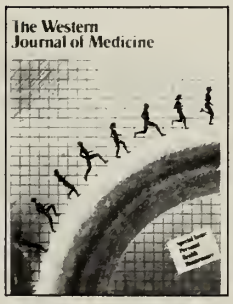
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



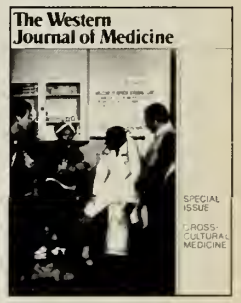
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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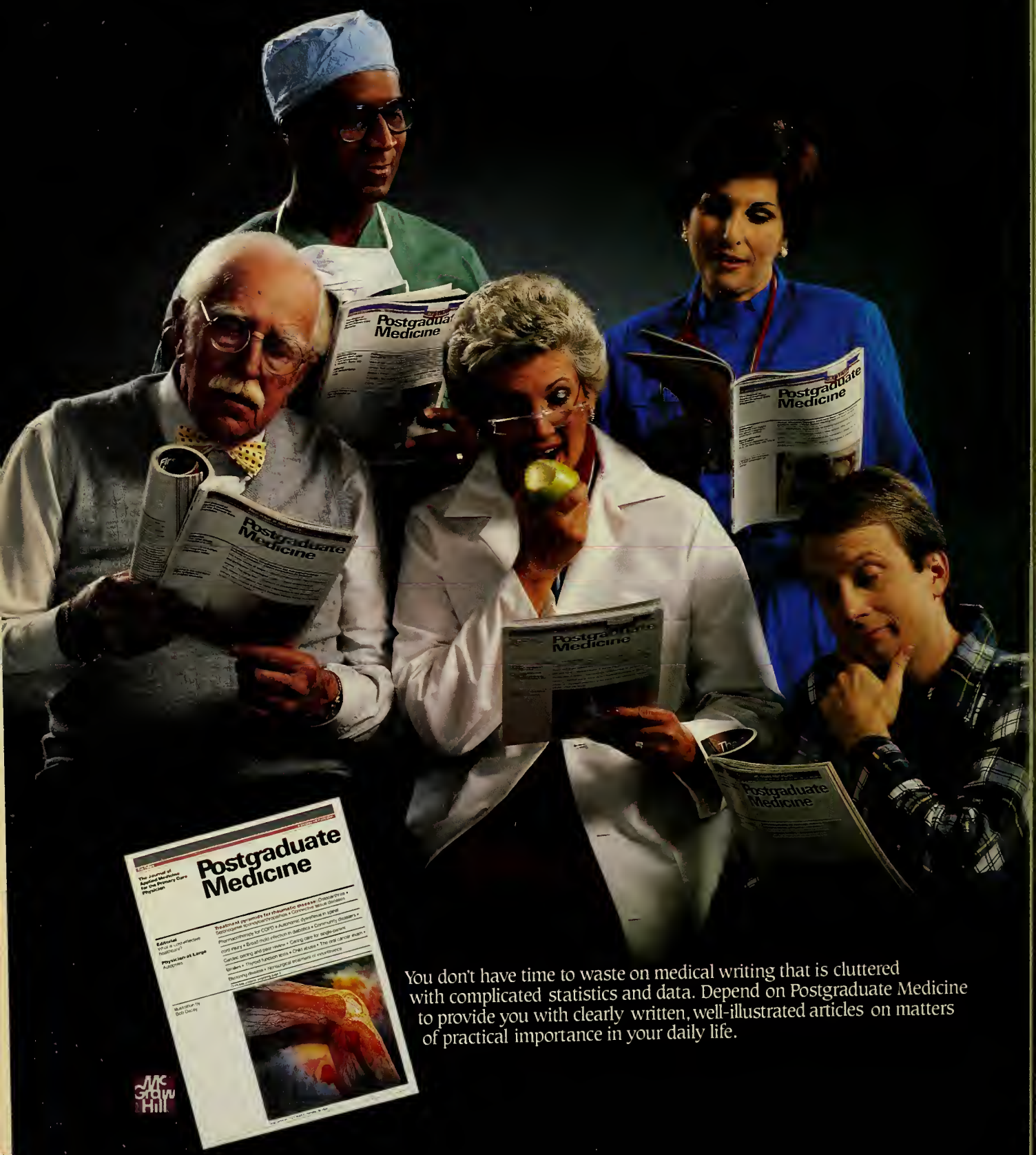

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

September 1989, VOL. XLVI, No. 9

Crunch Time—Are We In Or Out? Part I

Marshall B. Block, M.D.

A day does not go by without some headline appearing in either a local or national publication lamenting the increasing costs of health care and the need to control it. In concert with insurance companies and large employee corporations, the Federal Government is also trying to lasso the health care industry.

Over the last several years it has been the hospitals who have borne the brunt of these efforts. The development of the Perspective Payment System and DRGs for Medicare has resulted in significant diminution in hospital revenue. The development of state PROs for the Medicare system has diminished outlays for in-hospital care and improved its quality by eliminating both duplicate and unnecessary services. The resultant decline in the expenditures for hospital based medical care has been offset by increasing costs in the outpatient arena.

Physicians as a whole suffered little in this transition. Rather than treating patients in the hospital, outpatient care became the norm for many conditions. Outpatient surgical and radiological facilities grew in volume as well as in number. Physicians were for the first time directly involved in referring patients to for-profit facilities. In the past, most outpatient studies were done in outpatient *hospital* departments. The profit that heretofore was reinvested in hospital facilities was now available to others, including physicians. It was not surprising at all that Part B expenditures for physician services increased while Part A costs by comparison plateaued.

This increased physician reimbursement is now seen by our representatives as a clear mandate to limit federal expenditures in this area as well, even though it is unclear whether this increase can be justified by the greater involvement in outpatient activities precipitated by the Medicare rule changes. To this end, the House Ways and Means Committee has recently passed a bill which would target an amount Medicare will spend in the coming year for such services. This comes on the heels of the redistribution of physician reimbursement. The RBRVS system which will be implemented in 1991 will redistribute the available resources in a more equitable fashion to physicians based upon their cognitive skills.

In concert with these moves, the Health Care Finance Administration (HCFA) is going to assess the outpatient arena now that the hospital environment has been carefully monitored. A new initiative is going to be undertaken to assess how "effective" we are in our offices. A recent article appearing in the *NEJM* by then director of HCFA, William Roper, M.D., entitled "Effectiveness in Health Care" went relatively unnoticed. It proposed an initiative to evaluate and improve medical practice in the United States. "Federal health programs are no longer focused only on financing services, conducting biomedical research, implementing laws, and administering bureaucratic rules, but rather federal agencies will also be involved in the collection of data and the distribution of information about health care itself—information on health outcomes that will influence medical practices." Attempts are now underway to evaluate such a system using data from Medicare claims and from review of office based records.

It would appear that an arbitrary attempt to limit physician fees has been undertaken. At the same time a survey has been started to see whether the care rendered by physicians is effective. It is interesting that if effective health care is the goal of the Federal Government why would they choose to limit expendi

Continued on page 13

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In This Issue:

- Resource-Based Relative Value Scale: A Threat to Private Medicine
- Red Ribbon Campaign
- New Members
- Cardiac Resuscitation

Update on AIDS, AZ Liability Crisis

Two major meetings of interest and importance to physicians will take place this month in Phoenix. They deal with two of the issues which today have the most impact on the way physicians practice medicine: AIDS and the liability crisis.

First on tap is the hottest new name in liability circles: Washington, D.C., attorney Peter Huber, whose book "Liability: The Legal Revolution and Its Consequences" has rocked the legal world and offered a ray of hope to the beleaguered medical and business communities. Huber, who acknowledges at the start that his ideas are not going to please his legal fraternity brothers, breaks the mold and begins with the premise that there is indeed a liability crisis clogging the courts and threatening to shred the social fabric of America.

Huber's ideas center on the recent and dramatic change in the role and function of tort law. He explains the tort system was never intended to handle the bulk of disputes between individuals; never, that is, until the past three to four decades. In this short time period, he notes, we have drifted rapidly away from contract law that was historically designed to deal with conflict, the responsibilities of involved parties, and consequences for failure of either party to meet responsibility. He advocates an updated resurrection of contract law which he says can meet today's needs.

Because Huber's concepts -- unlike traditional tort reforms, such as those which have worked in California -- would not require a state constitutional amendment, they are particularly interesting in Arizona.

Peter Huber will speak at The Pointe at Squaw Peak, Phoenix, beginning at 9:30 a.m. Saturday, September 9, 1989. For tickets and further information, contact Susan Fuchs, Director of Communications, Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013, telephone 246-8901 in Phoenix or 1-800-482-3480 toll-free statewide.

An update on AIDS for health care professionals focuses on early diagnosis, initial and periodic evaluation and maintenance of HIV-infected patients. As the AIDS epidemic increases its toll on society, it becomes clear that early and appropriate medical care, combined with connection to community support systems, is critically important and that the human issues surrounding the disease extend far beyond basic diagnosis and treatment. The seminar addresses all those issues.

In addition to specific manifestations, early diagnosis and treatment, the seminar will include case presentations, ethics, legal issues and experimental protocols. Community organizations will exhibit their resources.

AIDS: Dimensions of Care -- An Update for Health Care Professionals will be held all day, 7:00 a.m. to 4:30 p.m., Saturday, September 16, 1989, at the Fountain Suites Hotel, Black Canyon Freeway (I-17) and Greenway Road, Phoenix. For further information contact Bev Gordon at the Arizona Department of Health Services, Office of Health Promotion and Education, (602) 255-1292. ■

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The Resource-Based Relative Value Scale: A Threat To Private Medicine

by Jane M. Orient, M.D.

Abstract

The resource-based relative value scale (RBRVS), currently favored by the Physicians' Payment Review Commission, is fundamentally flawed. It is based on the objective theory of value, which neglects the worth of a service to those who receive it. Although favored by groups that would tend to benefit in the short term, acceptance of the RBRVS is likely to cause divisiveness within the profession, interference in the physician-patient relationship, distortions in the medical marketplace, and other serious side effects.

"To Each What She Deserves": An Early Analysis

Would-be reformers of the Medicare payment system have resuscitated an old idea. The concept of a relative value scale, the "comparable worth" of medicine, was described and demolished in 1928 by George Bernard Shaw.

In his book *The Intelligent Woman's Guide to Socialism, Capitalism, Sovietism, and Fascism,* Shaw deplored an economic system that rewarded prizefighters so much more handsomely than others of presumed higher social value. "But to suppose that it could be changed by any possible calculation that an ounce of archbishop or three ounces of judge is worth a pound of prizefighter would be sillier still."[1]

Analyzing an example involving cognitive versus procedural skills, Shaw wrote: "Well think it out. The clergyman...is able to read the New Testament in Greek; so that he can do something the blacksmith cannot do. On the other hand, the blacksmith can make a horseshoe, which the parson cannot. How many verses of the Greek Testament are worth one horseshoe? You have only to ask the silly question to see that nobody can answer it."[1]

Objective vs Subjective Value: an Economic Analysis

The absurdity of trying to convert social value into an objective unit of measure such as ounces or horseshoes seems apparent from Shaw's examples. The resource-based relative value scale (RBRVS) attempts to circumvent this difficulty by expressing the value of a service in objective terms related to the cost of its production.

The method used by William Hsiao and colleagues at Harvard University considers four dimensions of physician work, including the time required to perform a service, the mental effort, the degree of technical skill, and stress.[2] The cost of production also includes the overhead expenses such as liability insurance. Although the Harvard study has been called "a significant new source of independent information from which to design a new Medicare payment system,[3] it is based on an old idea: the **objective theory of value**, one of the fundamental tenets of Marxist economics.

This theory, which is sometimes accepted as axiomatic, was subjected to critical scrutiny in the late nineteenth century by Austrian economists Carl Menger and Eugene von Böhm-Bawerk.[4] A simple example may serve to illustrate its fallacy:

Consider two diamonds of equal size and quality. Suppose that one was simply found by chance, with no effort or danger in its discovery, while the second one was recovered from a mine, representing a large investment by the owners, and significant danger to the workers. Although one diamond costs little or nothing, and the second was produced at enormous cost, both might be sold at the same auction for a similar price. In other words, there is no necessary connection between the value of an object and the cost of its production[5].

In fields characterized by rapid technologic advance, the fallacy of the objective theory of value is even more apparent. The theory would assign a higher value to one of the early mainframe computers, which occupied a large room, than to a far more powerful modern desktop computer, because the former cost far more to produce. Similarly, a lengthy cataract operation performed with great intensity of effort using old techniques should be valued more highly than a modern operation with lens implantation.

The objective theory of value considers only the producer and completely neglects the consumer. Nowhere does the calculation of "relative value" consider he most important factor: the benefit to the person who purchases the goods or services.

In contrast, the **subjective theory of economic value** proposes that the value of an object is not inherent in the thing itself, but exists in the mind of the person who values it.

As Bettina Bien Gaves pointed out, this theory "represented a completely new, revolutionary approach to economics. For the first time, the individual actor himself became the unit with which economics was concerned. His actions, his responses...were recognized as the key to explaining market phenomena."[6]

The ranking of values varies with each individual, depending on personal circumstances and expectations. A person may be willing to make great sacrifices to obtain certain services, but will purchase others only if they are very cheap.

For example, to one person cancer chemotherapy or surgery may seem a burden so great that the expectation of benefit may not be worth the price (either in money or suffering). To another, a small chance of cure may be worth any amount of pain and all of his worldly possessions. No third person can make a determination of the value of the service, even though its cost to the persons providing it may be exactly the same in the two instances.

According to the subjective theory of value, costs are basically **opportunity costs** incurred by a decision-maker, i.e. the value of the other goods or services he is willing to forego in order to obtain the goods or services under consideration. Such must be borne exclusively by the person making the decision; they cannot be shifted to another. Nor can they be measured by others, since subjective mental experience cannot be directly observed. (However, the subjective value is reflected in the price that an individual is willing to pay.) Further, costs are dated at the moment of final decision or choice.[7] An annual recalibration of the relative value scale is far too slow to account for changes in the personal circumstances of the actors in any economic transaction.

The objective theory of value must be assumed by those who believe in central planning by omniscient planners. The subjective theory of value is espoused by those who believe in economic freedom, in the rights of individuals to engage in voluntary transactions that they perceive to be of mutual benefit.

The Harvard Study: Specific Critiques

Although the Harvard study superficially appears to be objective, with its standard deviations, equations, and lists of numerical rankings expressed to three or four significant figures, it is based on physicians' judgments, which are inherently subjective. A study garbed in the statistical trappings of science tends to be highly impressive to policy-makers. However, when "judgments take the form of assigning fixed numerical weights and restrictive and arbitrary mathematical formulas to vaguely defined and unmeasurable concepts such as skill, intensity of effort, complexity, opportunity cost, and the allocation of overhead expenses, the results are castles built on sand."[8]

If the judgments are made by those with a consistent preexisting bias, then the results are probably built on quicksand. The group chosen by the Health Care Financing Administration (HCFA) to do the $2 million study had previously done work on this subject, with results that were procognitive and antiprocedural with respect to fee evaluations.[9,10] It is possible that HCFA determined in advance what it wanted, and got what it was paying for.

After obtaining a consensus from various specialists about the ranking of various procedures in order of difficulty, the researchers needed to normalize the results (i.e. rescale, compress and expand the rankings for different types of procedures so that they could be interlocked properly). The methodology to be used for this procedure was not specified. Dr. Robert Reinecke of Thomas Jefferson University Hospital thought that Hsaio's group might have withheld the details so as to prevent some specialists from jury-rigging the rankings to beat the system. However, in response to queries at an informational meeting in Dallas, Edmond Becker, Ph.D., Project Director for the Hsaio study, stated that the methodology had not been worked out, and that they planned to try different formulae until the data looked right. **This violates one of the most fundamental principles of research design, that the methodology must be specified before the data are collected.** It allows the researchers to manipulate the methodology until the data support their predetermined conclusions.[11]

After all the sophisticated manipulations, some of the results defied common logic. For example, the same relative value was obtained for a superficial lobectomy of the parotid gland as for a pharyngolaryngectomy for cancer. The latter procedure is far more exacting and requires much more post-operative care than the former. Another result that met statistical standards of reliability but failed the common-sense test was equating the intensity per unit time spent doing a diagnostic D & C with that spent performing a vaginal hysterectomy or managing a difficult labor.[12]

Who Favors the RBRVS?

Physicians who believe that their services are undervalued, and that they would therefore benefit from the RBRVS, are more likely to support the concept. The American Society of Internal Medicine (ASIM), the American Academy of Family Physicians (AAFP), the American Society of Anesthesiologists (ASA) and the American Academy of Pediatrics have been among the strongest advocates of an RVS.

The American Association of Retired Persons (AARP) is also promoting a change in the Medicare payment system based on the RBRVS. This strange ally of the ASIM and AAFP has a different long-range objective: forcing all physicians to accept assignment. At the present time, AARP concedes that there are certain inequities in the payment system. Once these are "corrected," there is no impediment to forcing the doctors to accept a payment that is certified to be "fair."

The concept of the RBRVS has long been promoted by labor unions, directors of health and welfare funds, and Blue Cross and other third party payers, as discussed by Robert J. Moorhead, former president of the Association of American Physicians and Surgeons (AAPS) in 1961.[13] The RBRVS would be a means of keeping fees in line, thus helping to save actuarially unsound

policies that offer first-dollar coverage.

The third parties themselves had difficulty developing an RVS for all medical procedures because of the obvious nonrelationship of so many procedures. They could not standardize the procedures when performed by more than one physician. Furthermore, they could not standardize patients. Thus, it was necessary to enlist physicians themselves to meet the "challenge" to relate, economically, all medical, surgical, x-ray, and laboratory procedures.

The American Society of Anesthesiologists set up a voluntary RVS in 1962. After it was in wide use for many years, the US Department of Justice entered suit in December, 1975, charging violation of Section 1 of the Sherman Antitrust Act. In June, 1979, the suit was dismissed. Ironically, now another unit of the federal bureaucracy is on the brink of instituting a mandatory RVS!

Pitfalls In Acceptance of the RBRVS

1. *Disunity in the profession.* Pitting one group against another (the "procedural" vs the "cognitive" or "nonprocedural" specialties) is an example of the time-honored technique of divide and conquer. Furthermore, the pursuit of financial self-interest can be self-destructive in the long term. Since the actual payment to the physician will be determined by the multiplier, not exclusively by the relative value, internists may find themselves worse off than before, despite a narrower gap between themselves and "proceduralists."

2. *Interference with the physician-patient relationship.* With the RBRVS, a collective tells every physician what his services are worth, and abolishes his right to contract with the individual patient. The RBRVS contradicts the basic principle of private medicine, that the unit of practice is the individual patient, and that the medical service is personal and unstandardized. (Note the critical difference between the RBRVS, which dictates the worth of a service, and an indemnity, which simply states what a particular insurer is willing to pay to its subscriber.) **The patients' values are completely excluded from the equations.**

3. *Next step: mandatory assignment.* Acceptance of the RBRVS transfers the onus of inadequate coverage to the physician, who is easily portrayed as a capitalistic gouger.[13] Members of the Physicians' Payment Review Commission have acknowledged that the RBRVS was likely to be followed by a nationwide ban on balance billing. While using terms like "equity," Congress is primarily interested in cost containment (i.e. a reduction in Medicare expenditures), which includes "controlling the inappropriate volume of care" (i.e. rationing.[14] An increase in the fee could easily be offset by disallowing more services as "medically unnecessary."

4. *Distortion in the medical marketplace.* Like all previous examples of wage and price controls, the RBRVS will predictably cause distorted market incentives, resulting in excesses and shortages. One proposed remedy is to maintain a dual system of fee schedule amounts and physicians' charges, so that average charges can serve as a continuous monitor of how closely the fee schedule reflects market conditions.[8] As all centrally planned economies have discovered, price information from a free market is absolutely essential to permit rational economic calculations.

While attributing undesirable incentives in the health care system to "distortions in the price of physicians' services" (caused by current third party payment schedules), Hsaio proposes that his fee schedule would serve as a corrective measure. Specifically, he suggests that central planners could use the RBRVS to encourage or discourage certain types of practice or behavior, to motivate physicians to serve in regions or specialties with shortages, and to identify outlying charges for closer peer review.[15]

5. *Encouragement of dishonesty.* Under the RBRVS, the physician would benefit from practices such as removing one wart at a time and filing a separate claim for each. This is to the patient's disadvantage and cannot be condoned. Neither can the establishment of the RVS, which precipitates this situation.[13]

6. *Irreversibility.* Like many steps on the road to collectivized medical practice, the RBRVS will be almost impossible to retract, once it is made public.

Conclusions

Because it is based on fallacious economics and flawed science, the RBRVS cannot correct inequities and distortions in the medical marketplace, but can only cause new ones. Its support is based on the politics of envy, which threatens to split the medical profession. While "proceduralists" and "nonproceduralists" war with each other over questions of short-term financial gain, the collectivization of medicine can proceed. The RBRVS gives would-be commissars a powerful tool for controlling the practice of medicine by controlling physicians' livelihoods. Its acceptance by physicians implies assent to the role of interchangeable servants of the collective, and a disavowal of responsibility to their patients as individuals.

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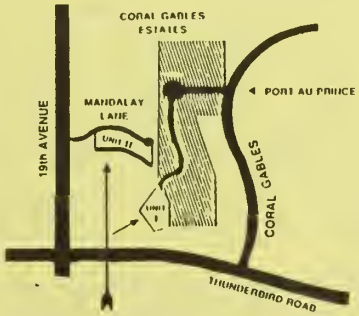

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Arizona Physicians Asked To Support 1989 Red Ribbon Campaign

Arizona's physicians have been asked to participate in the nation's second annual Red Ribbon Campaign, October 22-29, to focus public attention on America's drug abuse problem.

If present trends continue, in any given 40-student class graduating in the year 2000, two students will have given birth, eight will drop out of school, 11 will be unemployed, 15 will be living in poverty, 36 will have used alcohol, 17 will have used marijuana, 10 will have used cocaine, six will have run away from home and one will have committed suicide.

More than one out of five people in drug treatment today are teenagers -- or younger. About seven and a half million teens need treatment now for addictive illnesses, but fewer than 20 percent will actually get the help they need.

Statistics vary from source to source, but authorities agree that the majority of problems our children have are created by low self-esteem and drug abuse. We are in the midst of a drug abuse crisis.

That is why the National Federation of Parents and the Arizonans for Drug Free Youth conducted the first Red Ribbon Campaign last year, and why they're again coordinating a second campaign this year. The purpose of the campaign is to focus public attention on our drug problem and to mobilize communities to work together to solve local problems.

Physicians can help by wearing and distributing red ribbons to be worn by office staff and patients.

ArMA has ordered 6,000 red ribbons with the campaign's slogan, "Arizona's Choice: Drug Free!" and a physicians' logo, "D.A.D.D. -- Doctors Against Doing Drugs." D.A.D.D. Red Ribbon distribution is coordinated by the Arizona Medical Association Auxiliary, which has volunteered to handle the logistics.

Physicians are urged to distribute ribbons to office staff, patients and school classes. ArMA's first order of ribbons are free on a first-come, first-served basis to ArMA members. After they are gone, ribbons will cost $1 per five ribbons, with a minimum $5 order. The first 50 orders over $10 will also receive a free 12" by 18" red, white and gold poster that says "We support the 1989 Red Ribbon Campaign -- Arizona's Choice: Drug Free!" Deadline for ordering is September 30.

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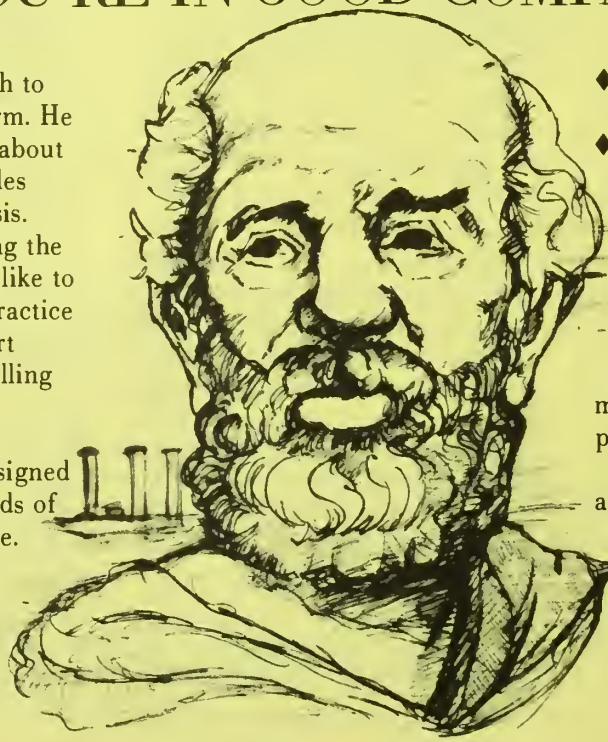

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988 Taxable Equivalent Yield Table for Arizona

axable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
ingle Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
)ver $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

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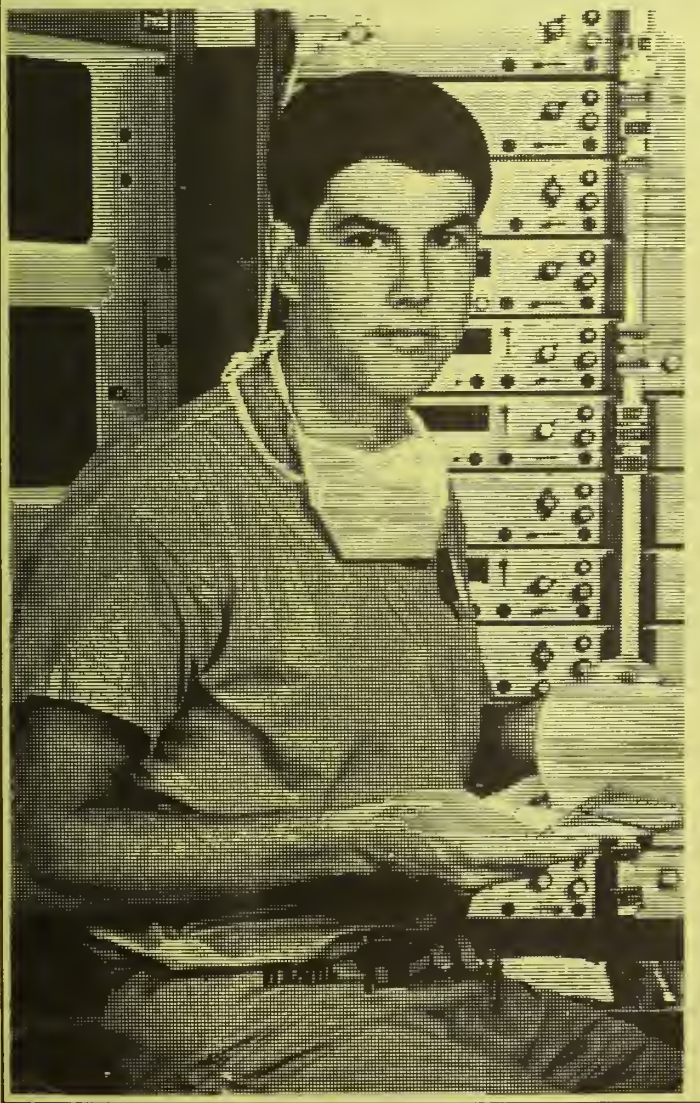

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Cardiac Resuscitation: New Insights

For years the techniques of basic (BCLS) and of advanced cardiac life support (ACLS) were known, and almost all of the efforts in the field were focused on disseminating the knowledge and skills of cardiopulmonary resuscitation (CPR) not only to the medical, nursing, and paramedic professions, but also to the lay community. The change in the BCLS and ACLS standards and the recent flurry of research into CPR techniques have been unsettling to those who were more comfortable when the standards were "written in stone." The dogma that there is only one way to do CPR in every adult patient is being seriously questioned. Our understanding of the mechanism of blood flow during CPR is evolving, and accordingly, techniques are being altered. Some traditional approaches are no longer thought necessary and others are now considered deieterious.

However, there is scientific data to support the following conclusions:

1. In patients with cardiac arrest secondary to ventricular fibrillation, the most important determinant of survival is the speed with which defibrillation is performed.

2. If immediate defibrillation is unavailable, basic cardiac life support applied immediately improves survival.

3. Patients who have cardiac arrest secondary to asystole or electrical mechanical dissociation are rarely resuscitated.

4. During resuscitation efforts, the most important drug to use is epinephrine.

5. Epinephrine works not by stimulating the heart, but by causing peripheral arterial vasoconstriction.

6. In some subjects compression rates of 100 to 120 per minute may be more effective than compression rates of 60 to 80 per minute.

7. The force of chest compression is an important determinant of basic CPR effectiveness.

8. The mechanism of blood flow during CPR is variable and depends not only on the subject, but also on physical characteristics of the CPR technique used.

9. The most important determinant of resuscitation success following prolonged CPR is the myocardial perfusion pressure, i.e. the pressure difference between the aortic "diastolic" pressure and right atrial "diastolic" pressure (during arrest and CPR "diastolic" is the relaxation phase of chest compression).

10. Since one can generate a good "systolic" blood pressure without a good "diastolic" pressure during CPR, the presence of a palpable pulse or an adequate systolic blood pressure does not assure adequate CPR techniques.

11. It is not possible to place arterial and right atrial catheters in the patient with cardiac arrest fast enough so that one can monitor hemodynamic and determine myocardial perfusion pressure.

12. During cardiac arrest, blood flow through the lungs is so slow that all of the carbon dioxide in the blood is released. The higher the blood flow, the higher the end-title carbon dioxide level will be. Therefore, monitoring end-expiratory carbon dioxide might provide immediate feedback as to the adequacies of techniques being used during CPR. Monitoring end-expiration carbon dioxide during CPR as a tool to determine the optimal CPR technique for each individual patient is being studied. ■

Gordon A. Ewy, M.D.
Chief of Cardiology
Professor of Internal Medicine
College of Medicine

Crunch Time

Continued from page 1

tures before assessing effectiveness? Obviously, the realities of the Federal budget outweigh at times philosophical questions and needs. Yet, even when one takes into account all of the above, there can still be some ray of hope on the horizon for medicine. If effective medical care can be attained at a lower cost per patient, then we should be in favor of accomplishing that goal. If we can look at a broad spectrum of medical problems and practitioners and assess patient outcomes, we might be in a better position to assess what is effective medical care. Without such information, much of what we do will always be an enigma. In our rapidly changing environment, we have to be able to support what we do with appropriate data.

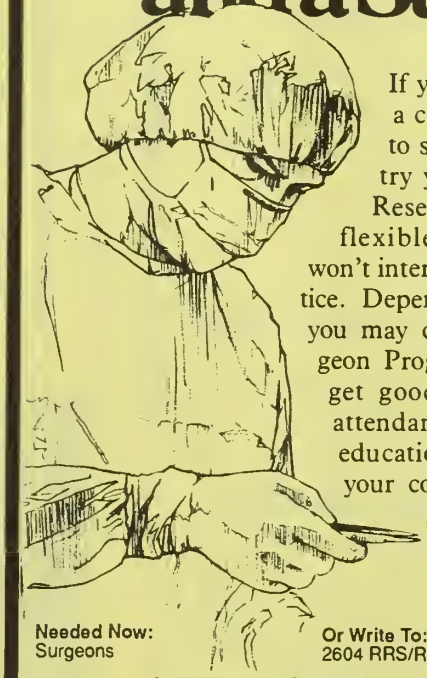
Perhaps it is a bit altruistic, perhaps it is a bit naive to think that knowing what is *effective* medical care will make us better physicians. However, two things are clear to me. Without making the effort we will not know the answers, and financial restraints will continue to be placed on the system. Unless we actively help define what is effective care, arbitrary decisions will be made that might not be in everyone's best interests. ■

Marshall B. Block, M.D.
Editor

Editor's Note: Part II will appear in the next issue of Arizona Medicine.

04 913-0039

An Officer and a Surgeon



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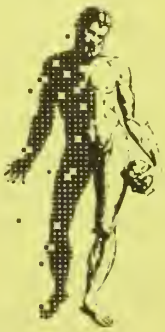

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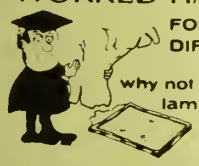

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Clinical Investigation

Clinical Responses With Active Specific Intralymphatic Immunotherapy for Cancer—A Phase I-II Trial

CHARLES L. WISEMAN, MD; V. SRINAVASA RAO, PhD, PharmD; PETER S. KENNEDY, MD; CARY A. PRESANT, MD; J. DOUGLAS SMITH, MD; *and* ROBERT J. McKENNA, MD, *Los Angeles*

We evaluated the method of active specific intralymphatic immunization to treat cancer in 32 patients with various tumor types as part of a broad-based phase I-II evaluation and describe the results of 3 sequential series. In series 1, the patients (n = 13) received 2 or more injections of autologous, cryopreserved, irradiated tumor cells directly into the lymphatic system through the cannulation of a dorsal pedal lymphatic channel. In series 2, the patients (n = 7) received low-dose cyclophosphamide, 300 mg per m^2, 3 days before the autologous cell vaccine was administered. Series 3 (12 patients) was similar to series 2 except that the tumor cells were treated with cholesteryl hemisuccinate immediately before irradiation. Patients received from 2 to 6 injections of cells, depending on availability, at 2-week intervals. In all, 91 treatments are evaluated in this study. Clinical responses occurred in 7 of the 32 patients and were seen in all 3 series with about the same frequency. These responses occurred in cases of melanoma, lung cancer, colon cancer, and sarcoma. Regressions occurred in both visceral and subcutaneous sites. There was little toxicity, the chief side effect being local discomfort or inflammation. This experience indicates that active specific intralymphatic immunotherapy is safe, produces antitumor effects, and requires more investigation to increase the frequency and duration of observable tumor regression.

(Wiseman CL, Rao VS, Kennedy PS, et al: Clinical responses with active specific intralymphatic immunotherapy for cancer—A phase I-II trial. West J Med 1989 Sep; 151:283-288)

The historical enthusiasm for using autologous tumor cells as immunogens has resulted in a number of clinical trials, and some positive results warrant further attention.[1] We have been interested in several recent developments that encourage further investigation of such an approach. We began a study to investigate and extend the original report of Juillard and co-workers, who described regression of metastatic tumors after inoculating irradiated tumor cells directly into the lymph nodes through the dorsal pedal lymphatic vessels.[2]

Direct intralymphatic immunization is an attractive concept for a number of theoretic reasons. Such a technique could circumvent possible immunosuppressive mechanisms of a primary tumor. Regional lymph nodes vary widely in immunologic responsiveness.[3] Some studies indicate that nodes close to a primary tumor have decreased functional competence and increased suppressor-cell activity as compared with nodes distant from the primary tumor.[4]

The intralymphatic approach has been studied in animals[5,6] with positive results and in several human tumor categories. In addition to the work of Juillard and colleagues, augmented immunologic responses were reported in breast cancer and in renal cancer by Adler and associates, although the clinical significance of these responses remains open.[7,8]

Our initial findings suggested that the method reproducibly elicited substantial biologic effects, with a significant elevation of the fraction (and absolute number) of circulating CD4+ lymphocytes. We observed that this elevation occurred after each immunization and in almost every patient.[9,10] In a few melanoma patients, two subpopulations of CD4+ were identified.[11]

Since the initiation of this study, we have made several modifications based on possibly useful newer techniques. The reports by Berd and Mastrangelo indicated that the use of low doses of cyclophosphamide may selectively block suppressor-cell functional activity, thereby leading to augmented specific immune responses.[12] After our initial experience, we introduced this as a pretreatment for our patients (series 2 and 3). We then changed the program in an attempt to increase potential cell-surface immunogenicity of tumor cells by reducing membrane-lipid microviscosity. We introduced the methods of Skornick and associates, using a brief incubation with cholesteryl hemisuccinate (series 3).[13]

Patients and Methods

Tumor Vaccine

Surgically removed tumor was dispersed by collagenase and deoxyribonuclease according to methods previously de-

From the Wilshire Oncology Medical Group (except Dr Rao), the Los Angeles Oncologic Institute, and the St Vincent Medical Center, Los Angeles.

This work was supported by the St Vincent Medical Center and the Wilshire Oncology Medical Group.

Funding in part was provided by the Auxiliary of the St Vincent Medical Center, the Ahmanson Foundation, the Zwick Fund, and the Los Angeles Oncologic Institute, a nonprofit philanthropic and research agency.

Reprint requests to Charles L. Wiseman, MD, 201 S Alvarado St, Suite A, Los Angeles, CA 90057.

scribed.[9] The cells were frozen slowly using a programmed cryogenic freezer (Union Carbide, Indianapolis) and stored over liquid nitrogen. On demand, the cells were thawed rapidly and washed in Hanks' medium. Adherent cells were removed by incubating at 37°C, and the remaining population was then irradiated to 200 gray from a cobalt 57 source. Dosimetry and supervision of the radiation procedure were provided by Armand Bouzaglou, MD, and John Sevilla, MD. For patients in series 3, vaccine preparation was modified. After thawing and washing, the cells were suspended in a polyvinyl pyrolidone-Hanks' solution, pH 7.2, containing 250 μg per ml cholesteryl hemisuccinate (Sigma), adjusted to 1×10^6 viable cells per milliliter, and incubated three to four hours at room temperature, washed, and resuspended in lactated Ringer's solution 5 to 10×10^6 viable cells per milliliter before irradiation. The irradiated cells were suspended in a lactated Ringer's solution at a concentration of 10 to 15 $\times 10^6$ viable cells per milliliter. Viability was assessed by trypan blue exclusion. Aliquots of the initial preparation and the irradiated vaccine were routinely tested for bacterial contamination by culture as recommended by federal protocol.[14] The viability of the tumor cells was generally about 70% or higher, although occasionally a patient was treated with a vaccine of lower viability.

Patients

All patients provided signed informed consent before enrolling in this program. Approval and periodic review had been provided by the Institutional Review Board of the St Vincent Medical Center (Los Angeles), both initially and after the sequential modifications of the program. All patients received a complete medical history and physical examination, complete blood counts, biochemical profile, and such x-ray films, computed tomograms, and isotope scans as needed to evaluate the extent of metastatic involvement and the dimensions of at least one measurable indicator lesion. Therapy was not initiated until at least three weeks had elapsed from previous chemotherapy, radiation therapy, or surgical procedure requiring general anesthesia. No additional antitumor therapy was permitted for any patient during the period of treatment on this protocol.

Autologous irradiated tumor cells, suspended at a concentration of 10 to 15×10^6 viable cells per milliliter, were injected over several minutes into a dorsal pedal lymphatic

TABLE 1.—*Clinical Characteristics of 32 Patients Receiving Active Specific Intralymphatic Immunotherapy*

Patient	Age, yr	Sex	Primary Cancer	ECOG Scale of Metastases*	Site(s) of Metastases	Previous Chemotherapy Regimens, No.
Series 1						
1	58	♂	Melanoma	1	Lung	0
2	45	♂	Melanoma	1	Lung, liver	0
3	76	♂	Melanoma	1	Nodes	3
4	26	♂	Melanoma	4	Skin	3
5	74	♂	Melanoma	4	Lung, liver	0
6	44	♂	Colon	4	Nodes, ascites, liver	1
7	26	♂	Colon	2	Liver	0
8	75	♀	Colon	2	Liver	1
9	54	♂	Lung	2	Lung	0
10	35	♂	Lung	1	Lung	0
11	41	♂	Nasopharynx	4	Liver, bone, lung	3
12	64	♂	Renal	1	Lung, chest wall	0
13	61	♂	Renal	2	Kidney	0
Series 2						
14	61	♂	Colon	2	Lung, abdomen	1
15	46	♂	Colon	1	Liver	0
16	32	♂	Melanoma	3	Liver, lung	0
17	46	♀	Melanoma	1	Skin	2
18	42	♀	Melanoma	2	Abdomen, nodes	1
19	48	♂	Renal	2	Lung	0
20	41	♂	Unknown	3	Abdomen, lung	1
Series 3						
21	64	♀	Colon	2	Liver, bone	1
22	52	♀	Lung	4	Skin, lung, kidney	1
23	78	♂	Lung	3	Lung, liver	0
24	68	♂	Melanoma	2	Abdomen	1
25	45	♂	Melanoma	2	Abdomen, nodes	3
26	56	♂	Melanoma	3	Scalp, liver, nodes	3
27	36	♀	Melanoma	2	Lung, nodes	0
28	32	♂	Melanoma	1	Lung	3
29	62	♂	Melanoma	1	Lung, skin	1
30	45	♀	Melanoma	3	Lung	2
31	65	♂	Renal	4	Bone, lung	3
32	45	♀	Sarcoma	2	Skin, liver	1

ECOG=Eastern Cooperative Oncology Group

*The ECOG scale measures the performance status of a patient using a scale of 0 (fully active, able to carry on all predisease activities without restrictions) to 4 (completely disabled, totally confined to bed or chair).

channel isolated after Evans blue was infiltrated and lidocaine hydrochloride was administered for local anesthesia according to methods used for lymphangiography. All cutdown procedures were done by the staff of the Department of Radiology, St Vincent Medical Center. Patients received the vaccine at two- to four-week intervals as supplies permitted. Unless required for other medical considerations, admission to hospital was not needed. For those patients receiving cyclophosphamide (Cytoxan, Bristol-Myers Oncology Division), the drug was injected intravenously three days before vaccine inoculation at a dose of 300 mg per m^2 following pretreatment with the intramuscular administration of triethylperazine, 10 to 15 mg (Torecan, Roxane Laboratories, Inc).

TABLE 2.—*Distribution of Tumor Types Per Series*

Tumor Types	Patients, No. Series 1	Series 2	Series 3	Total
Melanoma	5	3	7	15
Colon cancer	3	2	1	6
Lung cancer	2	0	2	4
Renal cancer	2	1	1	4
Miscellaneous*	1	1	1	3
Total	13	7	12	32

*Nasopharyngeal 1, adenocarcinoma of unknown primary 1, atrial myxosarcoma 1.

Results

The roster of patients, together with clinical characteristics, is provided in Table 1. As mentioned, our initial experience, series 1, represents the tumor vaccine program unmodified. Series 2 and 3 differ in that patients were treated with low-dose cyclophosphamide. Series 3 comprises those patients whose vaccine underwent pretreatment with cholesteryl hemisuccinate; additionally, series 3 patients, similar to the patients in series 2, received a priming, immunomodulating dose of cyclophosphamide before the vaccine treatment. There were 13 patients in series 1, 7 in series 2, and 12 in series 3. The program was initiated June 1, 1981; we evaluated responses and survival as of July 15, 1988. Table 2 shows the tumor types and their distribution according to series.

All patients had advanced cancer, usually with pulmonary or intra-abdominal metastases. The median age was 48 years (range, 26 to 78). There were 8 women. Eleven patients had had no previous therapy; an occasional patient had had extensive previous treatment. The median performance score on the Eastern Cooperative Oncology Group scale was 2; six had scores of 4 (completely bedridden) and five had

TABLE 3.—*Therapy and Responses*

Patient	Primary Cancer	Viable Cells/Cycle, × 10^6/ml	Tumor Response	Time to Progression, wk	Survival, wk	Comment
Series 1						
1	Melanoma	5.0, 25.0, 50.0, 56.0	Mixed	12.0	46.1	Partial remission, pulmonary; CNS failure
2	Melanoma	20.0, 15.0	Progression	4.0	13.0	
3	Melanoma	10.0, 14.0, 20.0	Progression	10.0	146.7	
4	Melanoma	20.0, 40.0	Progression	9.1	9.1	
5	Melanoma	10.0, 5.0, 35.0, 60.0, 20.0	Progression	12.3	13.1	
6	Colon	3.0, 6.0	Mixed	4.0	7.7	Regression of Virchow's node
7	Colon	6.0, 4.5, 4.8	Stable	19.7	24.0	
8	Colon	6.0, 9.0, 33.0	Stable	32.4	43.3	
9	Lung	10.0, 20.0, 12.0	Progression	9.0	19.1	
10	Lung	10.0, 2.0	Complete remission	22.7	43.1	See text
11	Nasopharynx	14.0, 8.0, 1.5	Progression	7.7	14.4	
12	Renal	20.0, 10.0, 30.0	Progression	10.0	299.4	
13	Renal	14.0, 14.0, 17.0	Progression	6.0	6.0	
Series 2						
14	Colon	10.0, 12.0, 10.0	Mixed	14.3	73.9	See text
15	Colon	11.0, 14.0, 14.0	Progression	8.3	169.4	Active, slowly progressive disease
16	Melanoma	20.0, 18.0	Progression	3.6	37.7	
17	Melanoma	16.0, 21.0, 12.5	Complete remission	67.9	79.0	See text
18	Melanoma	24.0, 28.0, 30.0	Stable	13.4	21.9	
19	Renal	12.0, 12.0, 13.0, 3.0, 7.0, 8.0	Progression	6.9	45.7	
20	Unknown	8.0, 9.0	Progression	7.0	9.9	
Series 3						
21	Colon	11.0, 6.0	Progression	7.0	15.6	
22	Lung	10.0, 9.7	Progression	4.6	6.1	
23	Lung	9.0, 9.0	Progression	7.0	19.3	
24	Melanoma	13.0, 9.0, 9.0	Progression	19.0	57.7	
25	Melanoma	10.0, 10.0, 10.0	Progression	10.0	59.3	
26	Melanoma	10.0, 12.0	Progression	5.7	6.4	
27	Melanoma	8.0, 8.0	Progression	12.4	17.1	
28	Melanoma	13.0, 13.0, 12.0, 10.0	Progression	9.0	38.7	
29	Melanoma	10.0, 10.0, 11.0	Partial remission	25.1	56.7	
30	Melanoma	8.0, 9.0, 9.0	Progression	6.9	13.1	
31	Renal	17.0, 16.0	Progression	4.4	11.9	
32	Sarcoma	11.0, 12.0, 14.0	Mixed	5.3	42.9	See text

CNS=central nervous system

scores of 3—that is, about a third of the patients were partially or completely bedridden.

Table 3 depicts the number of cycles of immunization per patient, the amount of viable cells of each vaccine treatment, the maximum response according to standard criteria of the Southwestern Oncology Group, the time to progression, and the duration of survival from the initiation of treatment. For 32 patients in the study, there were a total of 91 treatments. Examples of objective responses are depicted in Figures 1, 2, and 3. Figure 1 shows a chest x-ray film of patient 10, a 35-year-old man who underwent an exploratory thoracotomy for operable but not resectable, large-cell undifferentiated lung cancer. The patient received two vaccine treatments, with the subsequent disappearance of the lung nodule and improvement of mediastinal widening, both on chest x-ray film and computed tomography (CT). The patient was then treated by his referring physician with chemotherapy and irradiation to consolidate the remission, but the disease recurred five months later.

Figure 2 shows the computed tomograms of patient 29, a 62-year-old man who had an excisional biopsy of pulmonary nodules diagnostic of metastatic melanoma. In addition to pulmonary metastases, the patient had noticed a 1-cm nodule in the right thigh shortly before the initiation of vaccine treatment. The pulmonary disease showed regression, the thigh mass disappeared, and the patient had a reduction of serum concentrations to the monoclonal antibody CA 125 from 91 to 33 ng per ml eight weeks following the start of treatment. The patient then showed progressive disease in the lung and also brain metastases after six months.

Figure 3 shows CT scans taken of a 45-year-old woman (patient 32) who presented with an atrial myxoma invading the great vessels. After surgical resection she was treated with infusional chemotherapy with doxorubicin (Adriamycin, Adria Laboratories) hydrochloride, but hepatic metastases developed. She received three cycles of autologous irradiated tumor cell vaccine as per the methods described for series 3 patients. The follow-up scans five weeks later showed disappearance of several vaguely demarcated liver lesions and reduction of a major lesion from 4 by 4 cm to 1.5 by 1.5 cm. New lesions were identified on the skin and also in the lungs, but the hepatic lesions regressed.

Patient 1 had multiple vaguely defined pulmonary infiltrates, which showed more than 50% regression simultaneous with the development of brain metastases. Patient 14 had an exploratory laparotomy with partial resection of a retroperitoneal mass, not identifiable on computed tomography. Signs of a bowel obstruction developed 14 weeks later, again without tumor visible by CT scan. At an operation the patient had tumor obstructing the distal small bowel but the surgeon saw that the original tumor mass was more than 50% reduced.

Patient 17 had a resection of one of several large breast masses palpable and visible on mammography. After three vaccine treatments, the mass adjacent to the resected tumor appeared to enlarge and was resected. Interestingly, only necrotic debris was obtained. When the patient relapsed 68 weeks later, there was a large, palpable, and darkly pigmented nodule in the region from which a biopsy was previously taken, as well as several other areas in both breasts.

The median survival for all patients was 36 weeks. We note that occasionally a patient had an unusually long survival. Patient 12, with recurrent renal carcinoma in the chest wall, showed a greater than 25% increase in the size of the tumor; he was subsequently treated with a regimen of interferon, without significant benefit, then radiation therapy. Lung metastases also developed. Nonetheless, he remains ambulatory and reasonably active 299 weeks after the autologous intralymphatic vaccine therapy started. Patient 15 had progressive liver metastases on a CT scan after three treatments with autologous irradiated tumor cells and was treated with two courses of intrahepatic chemotherapy with mito-

Figure 1.—Left, A chest x-ray film of patient 10 before vaccine therapy shows a lesion **(arrow)** in the left hilum. **Right,** After 2 cycles, the left hilar lesion has disappeared.

mycin and fluorouracil. He has declined further medical evaluation but continues to work more than 169 weeks since treatment was initiated.

Direct toxicity was limited to an occasional local infection, rarely fever or other systemic reactions. There were no instances of regional adenopathy, nor did any patient have symptoms of immediate hypersensitivity. There was no evidence of tumor enhancement or acceleration of the clinical course. Wound infections and difficult cannulations were seen primarily in series 1 patients (three patients each). Fever was identified briefly in one patient, who received antipyretics and had a normal temperature after 24 hours. One patient (number 8) with colon carcinoma and extensive pelvic tumor had a self-limited deep vein thrombophlebitis in the contralateral leg; this condition required admission to hospital and anticoagulation but resolved without sequelae. The patient had no further complications until her demise from progressive distant metastases 32 weeks later. Another patient (number 13) with renal carcinoma died suddenly at home; at autopsy a pulmonary embolus was identified. This event is not unexpected in this population, but there is a possibility that the cutdown procedure, requiring immobilization on a guerney for 60 to 120 minutes, contributed to its development. Nonetheless, patients in the later series were not similarly affected.

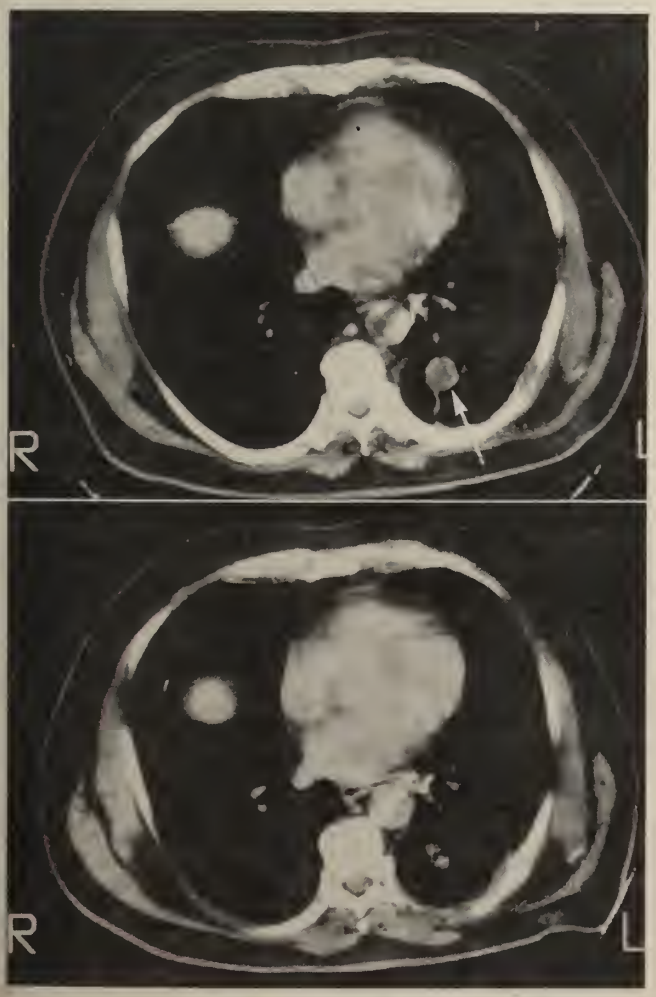

Figure 2.—Top, A computed tomogram at the start of treatment in patient 29 shows a large pulmonary nodule **(arrow)** in the left posterior lung. **Bottom,** A computed tomogram taken 60 days later shows regression of the nodule in the left posterior lung.

Discussion

This report confirms the clinical interest of active specific immunotherapy using autologous cells through intralymphatic injection. The original report by Juillard and colleagues in 1978 showed that tumor vaccines could elicit regressions of metastatic disease,[2] a controversial notion at a time when it was widely held that immunologic mechanisms would be ineffective except for subclinical, micrometastatic disease.[1] We describe here objective regressions in 7 of 32 patients studied. It should be noted that these very ill patients all had tumors for which effective or even palliative therapy is marginal. The responses have been limited and incomplete, however, and the problem of mixed responses is disappointing. McCune and co-workers, in a study of renal carcinoma, interpret mixed responses as a strong argument for the polyclonality of tumors.[15] The response of patient 32 is encouraging, even if there was growth of tumor at other sites, given the severity of liver involvement and the rarity of regressions under these circumstances.

In evaluating the population for possible prognostic factors, we note that all of the responding patients were younger than 65 and most had performance status scores of 2 or less. The mean age of the seven responders, however, was 50, and that age was not appreciably different from that of the group as a whole (mean age, 51.3 years).

Previous chemotherapy was not a contraindication to a response, contrary to the experience of Weisenburger and colleagues.[16] That study, albeit involving allogeneic tissue

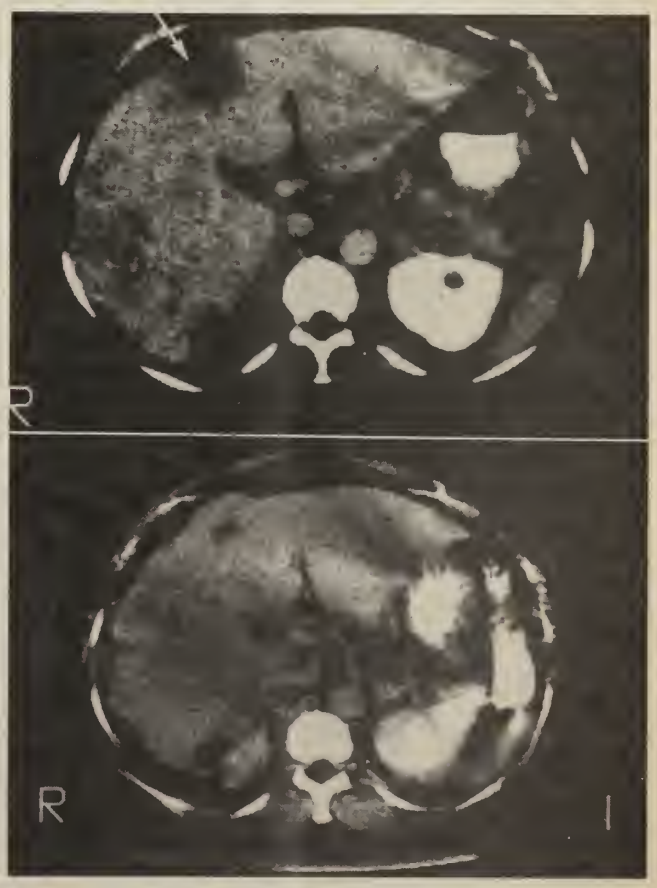

Figure 3.—Top, A computed tomogram taken of patient 32 shows an atrial myxoma **(arrow)** invading major vessels. **Bottom,** 70 days later, there is regression of the tumor nodule in the anterior lobe of the liver, with regeneration of liver tissue locally and in the posterior area of the right lobe.

culture cells, identified responses in 9 of 34 patients when intralymphatic therapy was the first method used but no responses in 13 patients who had received previous chemotherapy.[16] In contrast, five of our seven responders had previous chemotherapy.

Although we describe an evolving strategy for implementing active specific intralymphatic immunotherapy, the role of cyclophosphamide and of pretreatment of the tumor cells with cholesteryl hemisuccinate is still unclear. Skornick and associates reported responses in 7 of 21 patients treated with cholesteryl-modified autologous tumor cells.[17] This process did not amplify the response rate in our study. The incidence of clinical responses is not meaningfully different among the three series: 3 of 13 (23%) in series 1, 2 of 7 (29%) in series 2, and 2 of 12 (17%) in series 3.

The method and experience described suggest the existence of host responses that can have potentially useful effects against disseminated malignancy. Attempts to identify the existence of relevant serum antibodies, described by Ahn and co-workers[18] and by Fareed and colleagues,[19] have been unrewarding to date, both in our own laboratory and in an investigation by Karen G. Barnett, PhD, Hybridtech, Inc, San Diego (oral communication, September 1987). We have previously reported an initial impression that intralymphatic immunotherapy produces substantial augmentation of the CD4+ T-cell phenotype.[9,11] A further analysis indicates that this impression is confirmable,[20] and, notably, the more substantial increases of this subset also correlated significantly with the clinical response. Immunologic studies in progress may uncover or clarify further the underlying host-defense mechanisms and will be further evaluated in a separate report.

Our experience suggests that the method of intralymphatic immunotherapy is reasonably safe and technically feasible. It is hard to explain the regressions observed by mechanisms other than host immune responses engendered by the stimulus of the intralymphatic vaccine; understanding this process and modifying it to provide better and more durable responses remain a compelling challenge for further work.

Although one of us (C.L.W.) had previously initiated a similar program at a major academic center, we had some initial concerns about the feasibility of implementing this novel investigation at a community hospital. These concerns were not manifest in reality, and the community support of the program was gratifying. How best to further evaluate the method and to introduce it into clinical practice deserves attention. We are currently engaged in a clinical trial to evaluate a possible role for interleukin 2 in conjunction with this technique of active specific intralymphatic immunotherapy.

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Total and High-Density Lipoprotein Cholesterol Measurements

Hazards in Clinical Interpretation

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Duplicate plasma specimens from 24 persons were sent to a community hospital, a commercial laboratory, and a university lipid research laboratory at two separate times to assess the intralaboratory and interlaboratory variations of total and high-density cholesterol measurements. For all three laboratories, the 95% confidence limits for the reproducibility of total cholesterol levels are about ±5.5%. For high-density lipoprotein (HDL) values, they are ±7%, ±14.45%, and ±9%. Interlaboratory differences for total cholesterol at the 95% confidence level are ±7.7% and for HDL ±18.4%. Construction of a "cardiac risk ratio" of total to HDL cholesterol levels is subject to confusion because small errors in HDL cholesterol levels produce large errors in the ratio.

(Rivin AU: Total and high-density lipoprotein cholesterol measurements—Hazards in clinical interpretation. West J Med 1989 Sep; 151:289-291)

More than 30 years ago we published an article, "Serum Cholesterol Measurement—Hazards in Clinical Interpretation,"[1] that dealt with the weak reproducibility of the total cholesterol measurement, the pronounced interlaboratory variation, and the dangers of drawing clinical conclusions from such data.

Now that there is general acceptance of the total cholesterol level as an important risk factor for coronary artery disease[2] and the portion of the total cholesterol in the high-density lipoprotein fraction (HDL) as a "protective factor" against coronary disease,[3] it would be of interest to check again on how representative laboratories are doing. With the National Cholesterol Education Program (NCEP) heightening the awareness of physicians and the public, we need to know the reliability of our reported measurements.

Methods

Blood specimens were taken from 21 volunteers and 3 outpatients who were seated and in a nonfasting state, and the specimens were placed in ethylenediaminetetraacetate tubes. Plasma specimens were frozen and stored at −20°C. An aliquot of the first specimen of each duplicate was submitted to three laboratories: a community hospital (A), a commercial laboratory (B), and a university hospital lipid research laboratory (C) for total and HDL cholesterol measurements. A month later the remaining frozen plasma aliquots were sent to the three laboratories for the same measurement on the duplicate specimens.

Laboratory C uses the Centers for Disease Control-Lipid Research Study methods for measuring total cholesterol levels.[4] Laboratory A uses the method described by Allain and co-workers with the Abbott reagent system and the Coulter Dacos analyzer.[5] Laboratory B uses a similar method with a SMAC instrument and Technicon reagents. Levels of HDL in all laboratories were measured by precipitating the low-density lipoprotein and determining the amount of HDL cholesterol in the supernatant.[6] Plasma measurements of total cholesterol are known to be 3% lower than those found in serum.[7]

Results

All results are listed in Table 1.* Table 2 lists the mean of each measurement by laboratory and replicate. Table 3 shows the components of error and 95% confidence intervals for each laboratory measurement. The last column of Table 3 selects a total cholesterol value of 200 mg per dl and an HDL level of 45 mg per dl as representative and shows the ranges for each of these at a 95% confidence interval for each laboratory. Table 4 shows the interlaboratory variation when they are chosen successively at random. The error is computed for two components: day-to-day variation and basic assay variation on replicates done on the same day. The combined error (assuming they are independent) is then estimated at 95% confidence intervals.[9(p359)]

Discussion

The intralaboratory precision and interlaboratory difference for measuring total cholesterol levels have improved remarkably in the 30 years since our first study when errors of 25% within the laboratory and 100% between laboratories were common. As seen in Table 3, at least these three laboratories have nearly achieved the "acceptable goal" as determined by the Laboratory Standardization Panel of the National Cholesterol Education Program of ±5% coefficient

*The cholesterol levels in this article were reported by the three laboratories in conventional units and were not converted to Système International (SI) units as to do so would risk distorting the information. To convert a total or high-density lipoprotein cholesterol value from milligrams per deciliter to millimoles per liter, multiply by 0.02586.

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
NCEP = National Cholesterol Education Program

of variation,[10] and, yet, a total cholesterol level of 200 mg per dl might be read as 190 to 210 mg per dl (Table 3). The accuracy or performance against a standard provided by the College of American Pathologists or the National Committee for Clinical Laboratory Standards was not tested in this study.

TABLE 1.—*Total Cholesterol (TC) and High-Density Lipoprotein (HDL) Levels and TC:HDL Ratio Replicates From 3 Laboratories, in Milligrams per Deciliter*

	Laboratory A Cholesterol Values			Laboratory B Cholesterol Values			Laboratory C Cholesterol Values		
Specimen	Total	HDL	TC:HDL	Total	HDL	TC:HDL	Total	HDL	TC:HDL
1	175	26	6.7	190	25	7.6	178	23	7.7
	179	28	6.4	181	22	8.2	179	25	7.1
2	171	31	5.5	194	32	6.1	182	33	5.5
	184	34	5.4	194	27	7.2	179	33	5.4
3	146	48	3.0	164	48	3.4	154	53	2.9
	152	51	3.0	161	40	4.0	153	49	3.1
4	141	39	3.6	156	40	3.9	168	40	4.2
	148	42	3.5	152	35	4.3	145	40	3.6
5	229	71	3.2	249	68	3.7	241	75	3.2
	239	74	3.2	243	62	3.9	227	68	3.3
6	140	53	2.6	155	49	3.2	151	55	2.7
	146	56	2.6	158	38	4.2	145	52	2.8
7	171	36	4.8	193	30	6.4	196	33	5.9
	175	39	4.5	197	24	8.2	183	37	4.9
8	167	32	5.2	186	33	5.6	174	31	5.6
	170	36	4.7	184	29	6.3	175	32	5.5
9	171	77	2.2	190	77	2.5	176	80	2.2
	181	81	2.2	190	67	2.8	181	76	2.4
10	169	43	3.9	189	44	4.3	173	49	3.5
	179	46	3.9	187	37	5.1	185	46	3.8
11	171	69	2.5	190	69	2.8	175	76	2.3
	180	72	2.5	194	62	3.1	178	71	2.5
12	148	46	3.2	164	44	3.7	157	49	3.2
	152	49	3.1	164	41	4.0	154	48	3.2
13	200	43	4.7	218	43	5.1	207	47	4.4
	211	47	4.5	221	39	5.7	215	44	4.9
14	204	48	4.3	226	48	4.7	212	50	4.2
	214	51	4.2	220	42	5.2	220	48	4.4
15	206	80	2.6	227	75	3.0	216	80	2.7
	215	83	2.6	230	68	3.4	217	78	2.8
16	193	87	2.2	217	81	2.7	201	92	2.2
	207	89	2.3	219	75	2.9	202	87	2.3
17	132	42	3.1	150	38	3.9	140	45	3.1
	141	45	3.1	148	38	3.9	141	43	3.3
18	125	38	3.3	147	37	4.0	139	43	3.2
	135	41	3.3	140	35	4.0	139	40	3.5
19	191	36	5.3	201	34	5.9	183	38	4.8
	192	39	4.9	204	31	6.6	189	40	4.7
20	261	56	4.7	268	56	4.8	247	56	4.4
	255	60	4.3	259	50	5.2	252	57	4.4
21	253	50	5.1	273	51	5.4	260	52	5.0
	257	53	4.8	270	43	6.3	259	52	5.0
22	165	52	2.9	143	30	4.8	160	52	3.1
	158	53	3.0	144	30	4.8	156	50	3.1
23	253	33	7.6	227	29	7.8	244	34	6.1
	248	33	7.5	231	28	7.9	237	32	6.1
24	298	33	9.0	293	32	9.0	289	33	8.7
	304	32	9.5	262	34	7.7	288	36	8.0

Interlaboratory comparability was tested in this study, and there is a clear tendency for laboratory A to record the lowest total cholesterol values, laboratory B to record the highest, and laboratory C to be in between. Laboratory A has a serious shift between the duplicate runs in both total and HDL cholesterol levels. Laboratory B has a larger shift in HDL, and laboratory C is more consistent (Table 2). The between-laboratory variance is ±7.7%, and, at a level of 200 mg per dl, the range is 186 to 215 mg per dl (Table 4). An example of interlaboratory variation is seen with specimen 24 (Table 1) in which the total cholesterol was recorded as high as 304 mg per dl in laboratory A and as low as 262 mg per dl in laboratory B. Because the Lipid Research Study says

TABLE 2.—*Mean Total Cholesterol (TC) and High-Density Lipoprotein (HDL) Values and TC:HDL Ratios by Laboratory and Replicate in Milligrams per Deciliter*

		Cholesterol Level		
Laboratory	Replicate	Total	HDL	TC:HDL Ratio
A	1	181.9	46.2	3.94
	2	188.3	48.8	3.85
B	1	196.5	43.8	4.49
	2	194.4	39.3	4.95
C	1	188.9	47.9	3.94
	2	187.7	47.0	3.99
Mean		189.6	45.5	4.19

TABLE 3.—*Components of Error and 95% Confidence Intervals for Levels of Total Cholesterol (TC) and High-Density Lipoprotein (HDL) and TC:HDL Ratios**

		Component		95%	
Chemistry	Laboratory	For Day	Replicate	Interval, %	95% Interval
					200-mg/dl Report
Total Cholesterol	A	2.92	3.99	± 5.22	190-200
	B	0.92	5.20	± 5.57	189-211
	C	0.00	5.45	± 5.74	189-211
					45-mg/dl Report
HDL	A	1.35	0.85	± 7.00	42-48
	B	2.40	2.25	±14.45	39-51
	C	0.67	1.93	± 9.00	41-49
TC:HDL	A	0.047	0.139	± 7.01	
	B	0.222	0.400	±21.84	
	C	0	0.262	±12.51	

*STATISTICAL NOTE: Analysis of variance computations, using the method described by Dixon and Massey,[6(p355)] provided estimates for each of the 3 laboratories of the variability associated with each of the variables: patient, first or second specimen (day), and individual patient-to-patient variation. The error for a reported value will then have a standard error—that is, the square root of the sum of squares of the two components. Because an error in a cholesterol measurement is approximately proportional to the level of the reading, we convert these to the percentage of the average level reported by each laboratory and multiply by 1.96 to form an approximate 95% confidence interval. These percentage intervals are then related to a 200-mg/dl level for total cholesterol and to a 45-mg/dl level for high-density lipoprotein. For Table 4 we include, in a similar way, the component for laboratory-to-laboratory variability. We now have the expected variability for all three sources of variation: day-to-day variation, laboratory-to-laboratory variability, and the error for an individual assay that applies when a particular laboratory and a day to send the specimen are chosen. The statistical analyses were done by W. J. Dixon, PhD, The Dixon Group, Los Angeles.

TABLE 4.—*Interlaboratory Variation at 95% Confidence Interval for a Random Selection of Laboratories**

Chemistry	95% Interval, %	Range at Selected Level of 95% Confidence
Total cholesterol	± 7.7	200 mg/dl: 186-215
HDL	±18.4	45 mg/dl: 38-53

*See footnote on Table 3 for an explanation of the statistical analyses.

that for every 1% drop in the total cholesterol level there is a 2% drop in cardiac risk,[11,12] a physician receiving a report of 304 mg per dl would be pleased with the effectiveness of treatment if the next specimen was sent to laboratory B and received a report of 262 mg per dl. Without an awareness of the interlaboratory variation on duplicates, that physician might conclude that he or she had reduced the patient's risk by 20%.

With the great emphasis on HDL cholesterol as a "protective factor" against coronary artery disease and the statement that for every 5-mg-per-dl decrease in HDL below 45 mg per dl, there is an increased risk of 25%,[13-15] clinicians should be warned that there may be considerable variation on this test: ±7% in laboratory A, ±14% in laboratory B, and ±9% in laboratory C. For example, reports from laboratory B on duplicate plasma show differences of 5 mg per dl or more in 14 of the 24 specimens. Even in the university laboratory C, there are two examples of a variance of 5 mg per dl or more. The interlaboratory variation is ±18.4% and, at a level of 45 mg per dl, the range is 30 to 53 mg per dl. Care should be taken in interpreting a substantial change in an HDL-cholesterol value that may be due only to laboratory error.

The commonly used "cardiac risk" ratio of total to HDL cholesterol[3] magnifies the precision error of small changes in the HDL. In laboratory B's results for specimen 2, with the same cholesterol value of 194 mg per dl, HDL levels on the duplicates are reported as 32 mg per dl and 27 mg per dl, resulting in ratios of 6.1 and 7.2. Clinicians might worry if under their care the ratio increased unfavorably in this way if they were unaware that in this laboratory duplicate specimens were read with this difference. A similar duplicate reading error is noted in laboratory C, specimen 7, where a total cholesterol level of 196 mg per dl and an HDL value of 33 mg per dl resulted in a ratio of 5.9 and a total cholesterol of 183 mg per dl and an HDL value of 37 mg per dl gave a ratio of 4.9. In laboratory B, a report of an HDL of 45 mg per dl may actually represent a range of 39 to 51 mg per dl (Table 3). Other investigators have done similar studies and found a substantial variation from laboratory to laboratory.[16,17] The most striking is the College of American Pathologists' study in 1984 in which, using a cholesterol standard of 262 mg per dl, results of 108 to 545 mg per dl were reported.[18] Recent data from their proficiency testing survey indicate an average intralaboratory precision of ±3.5% and an interlaboratory comparability of ±6.2%.[10]

Conclusion

The intralaboratory replication of total cholesterol levels (precision) has improved considerably in 30 years. The three laboratories tested here come close to the NCEP acceptable level of ±5% for conventional units (milligrams per deciliter). There is enough variation in total cholesterol results from laboratory to laboratory, however, to encourage all laboratories to set up their procedures and their normal ranges according to the Lipid Research Study-Centers for Disease Control standards,[19,20] so that they would be interpretable across the country in a uniform way. The measurement of HDL levels is especially subject to error, and conclusions about coronary artery disease risk according to the ratio of total to HDL cholesterol levels magnifies the importance of small changes in the HDL fraction.

Until these changes are made, one reliable laboratory should be used consistently because sending specimens to two or more laboratories might lead to false assumptions about a change or a treatment effect. The laboratories should provide a statement about the expected variability of their result at the 95% confidence level, and they should participate in and report their accuracy in the standardization and quality trials provided by the American College of Pathologists or the Centers for Disease Control, Clinical Chemistry Standardization, the National Committee for Clinical Laboratory Standards Reference System for Cholesterol (or both).

Eight laboratories across the country have been set up by the NCEP to accept split-specimen analysis to check on the accuracy of local laboratories. The names and addresses of these laboratories can be obtained from the National Heart, Lung, and Blood Institute's Information Center, University Research Corporation, 5530 Wisconsin Ave NW, Suite 1600, Chevy Chase, MD 20815, telephone (301) 951-3260.

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Penicillinase-Producing *Neisseria gonorrhoeae* in California

Report of a Major Outbreak and Control Recommendations

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A major outbreak of penicillinase-producing Neisseria gonorrhoeae *occurred in California beginning in late 1986. After a state public health emergency was declared in April 1987, a statewide, cooperative federal-state-local treatment and control program was implemented. It was successful in reducing the reported incidence by 59%. Despite the success of this effort, penicillinase-producing* N gonorrhoeae *is not controlled in California, and, while not nearly the magnitude reported in Florida, an increasing number of cases are again being reported in California. We present recommendations for clinicians and local public health officials, including the epidemiologic and empiric treatment of suspected gonorrhea cases with ceftriaxone when the incidence of penicillinase-producing gonococcal cases in a community exceeds 1% of all reported gonorrhea cases.*

(Kizer KW, Felten JA, Jodar VA, et al: Penicillinase-producing *Neisseria gonorrhoeae* in California—Report of a major outbreak and control recommendations. West J Med 1989 Sep; 151:292-295)

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) was first reported in the United States and in California in 1976 among military personnel returning from the Philippines.[1] Although the exact origin of the penicillinase-producing gonococci is unknown, the wide use of broad-spectrum oral antibiotics in the Far East and the probable transfer of β-lactamase plasmids from enteric bacteria to *N gonorrhoeae* are thought to have played a role in its evolution.[2] After its sudden appearance among military personnel in California, PPNG remained under control until 1980, when its incidence among military personnel doubled and the number of civilian cases increased tenfold (Figure 1).

During a 16-month period in 1980-1981, the nation's first major civilian-originated PPNG epidemic occurred in Los Angeles County.[3,4] By 1982 when this outbreak was brought under control, 675 cases of PPNG had been successfully detected and treated with the aid of temporarily assigned state and federal disease investigators. The number of diagnosed cases in this outbreak alone exceeded that of all cases previously reported from California.

After the 1980-1981 outbreak, the number of cases reported annually in California rose by about 50% per year, primarily because of frequent prostitute-linked outbreaks among Hispanics in the agricultural Central Valley and among blacks and Hispanics in major metropolitan areas.

From 1982 through 1986, there were 28 known PPNG outbreaks in California involving several hundred cases in 12 local health jurisdictions. Despite the frequency of the outbreaks, state and local public health agencies were able to control them with existing manpower. As shown in Figure 2, however, beginning in the summer of 1986 dramatic increases in the number of reported cases signaled a widespread outbreak in California, with most cases being reported from Los Angeles County and other southern California counties. By the end of 1986, PPNG reached endemic thresholds of 1% of all reported gonorrhea cases in more than a dozen California health jurisdictions.

Recognizing the magnitude of the problem in California and being cognizant of similar situations in New York and Florida where PPNG had become endemic, the California Department of Health Services (CDHS) declared a state public health emergency in April 1987. This declaration authorized increased funding for the purchase of more PPNG-specific antibiotics and the initiation of other control efforts. The subsequently implemented PPNG treatment and control program was a cooperative state-federal-local effort that seems to have been effective in combating an unprecedented spread of the disease in California. We describe here the general characteristics and details of this effort.

California's PPNG Treatment and Control Program

Choice of Drug

After declaring a public health emergency, CDHS had to decide which antimicrobial agent to use in the PPNG treatment and control program. Two agents, ceftriaxone sodium and spectinomycin hydrochloride, were considered. Each is effective in treating PPNG,[5] but ceftriaxone has three additional advantages: it is effective against gonococcal infection of the nasopharynx, which is otherwise difficult to eradicate[6-8]; it may abort incubating syphilis[5]; and it is effective against chancroid.[9]

Ceftriaxone's effectiveness against pharyngeal PPNG

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
PPNG = penicillinase-producing *Neisseria gonorrhoeae*
STD = sexually transmitted disease

eliminates the need for at least one additional culture per patient and reduces the need for follow-up and retreatment. Furthermore, because epidemiologic studies have confirmed the presence of multiple sexually transmitted infections among high-risk groups,[10] ceftriaxone's efficacy in treating chancroid and the possibility of the drug having an effect against incubating syphilis were considered additional advantages. Because savings in laboratory and epidemiologic investigation costs more than offset the additional cost of ceftriaxone, it was selected as the antimicrobial agent for this program.

Strategy

The use of ceftriaxone in treating gonorrhea was but one element in the overall strategy of the program. The experience gained from managing dozens of sexually transmitted disease (STD) outbreaks during the previous 15 years in California had clearly shown that success in such efforts depends on coordinating a wide variety of complementary activities at the program management, laboratory, clinic, and community levels. Therefore, at the outset of the statewide control program in 1987, specific activities and roles were outlined in a letter to local health officials. In brief, this cooperative strategy called for the following:

- Expanded laboratory testing;
- Expanded treatment protocols to include criteria for epidemiologic and empiric treatment;
- Issuance of a medical alert for physicians, other practitioners, and laboratories at the local level;
- Active epidemiologic surveillance, data collection, and reporting; and
- A testing and treatment program in jails.

At the same time, the letter described the reciprocal responsibilities of CDHS, including providing technical assistance.

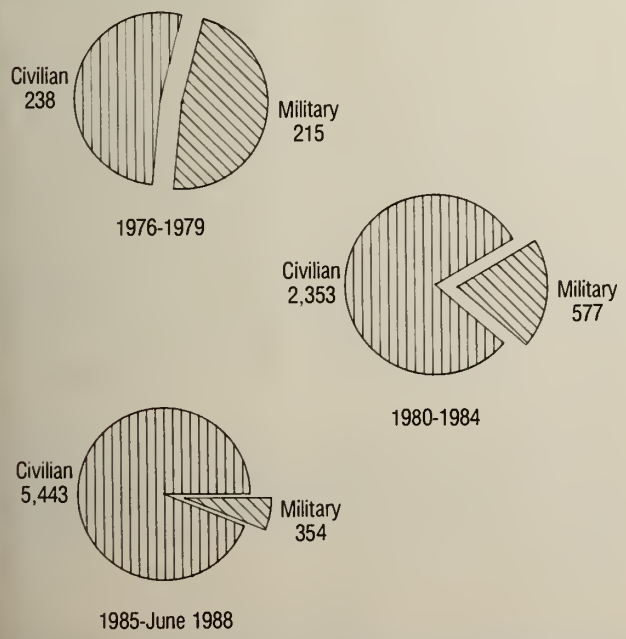

Figure 1.—The penicillinase-producing *Neisseria gonorrhoeae* in military versus nonmilitary persons from 1976 to June 1988, reported to the California Department of Health Services, are shown.

Results

The PPNG treatment and control program was fully operational by July 1987, and during the ensuing months the medical personnel in 18 participating local health jurisdictions administered ceftriaxone to 21,249 PPNG patients and high-risk persons (Table 1). By March 1988, the incidence of PPNG had been reduced to levels seen in early 1986.

Activities during the July to December 1987 program period were closely monitored. During that time, an average of 2,700 patients with PPNG and high-risk persons per month received ceftriaxone. High-risk categories were based on the groups that had been identified during the earlier outbreaks in California. Of 16,109 persons treated with ceftriaxone during this first six months, two thirds (11,049) were men. In addition, 2,704 (17%) either were prostitutes or had sexual exposure to them. Also during this time, local laboratories did more than 9,000 gonorrhea cultures and tested nearly 2,000 specimens for β-lactamase production per month.

Before the official commencement of the program in mid-1987, some larger local health jurisdictions were implementing selected program components and achieving limited results (Figure 2). It was clear, however, that such individual actions were not controlling the outbreak.

By the end of the formal state of emergency in March 1988, PPNG morbidity had been reduced 59%, or to about 150 cases per month. The most precipitous drop occurred during October to December 1987, when all 18 participating jurisdictions operated at full capacity and produced a statewide PPNG morbidity decrease of 41%. Overall, in 12 of the 18 local jurisdictions, PPNG morbidity decreased substantially, including in the 5 jurisdictions that together reported three fourths of all cases at the peak of the outbreak. In these 5 jurisdictions, morbidity was reduced by 64%.

The most strategic health jurisdiction continues to be Los Angeles County, which accounted for 61% of California's cases of PPNG at the height of the outbreak and which has been a nidus of infection since PPNG was first introduced into the United States. Los Angeles County also had the greatest reduction in morbidity—68%.

Discussion

Penicillinase-producing *N gonorrhoeae* is characterized by the production of β-lactamase, an enzyme that inhibits the effectiveness of penicillin. In fact, PPNG is resistant to peni-

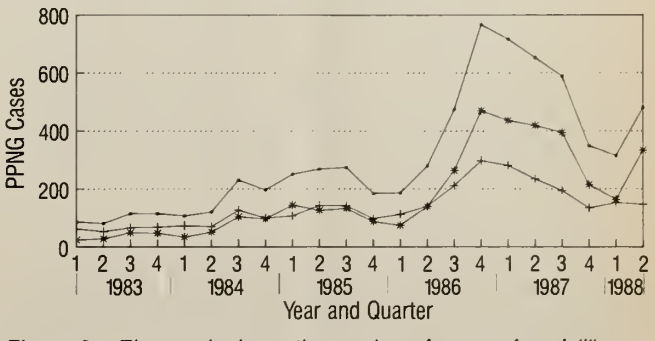

Figure 2.—The graph shows the number of cases of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in California from January 1983 through June 1988 reported to the California Department of Health Services. • = state total, + = all other, ⋆ = Los Angeles County

TABLE 1.—*PPNG Morbidity Before and During the California Department of Health Services (CDHS) PPNG Treatment and Control Program*

Participating County	Number of Persons Treated With Ceftriaxone, 7/1/87-3/31/88	PPNG Morbidity						
		July to Sept 1986	Oct to Dec 1986	Jan to March 1987	April to June 1987	July to Sept 1987	Oct to Dec 1987	Jan to March 1988
Fresno	1,490	2	4	22	6	12	5	6
Kern	1,440	4	8	1	2	1	2	0
Long Beach	1,230	26	63	50	27	12	13	11
Los Angeles	4,229	263	470	436	419	395	215	163
Orange	2,128	59	40	26	29	21	10	15
Riverside	66	0	6	2	13	7	5	1
Sacramento	1,182	9	22	15	11	0	2	5
San Bernardino	1,086	2	29	9	6	6	8	17
San Diego	1,875	44	47	85	61	60	44	56
San Francisco	3,408	7	15	15	9	11	8	12
All other jurisdictions	3,156	58	63	55	72	64	35	29
State	21,290	474	767	716	655	589	347	315

PPNG=penicillinase-producing *Neisseria gonorrhoeae*

cillin, which has been the most commonly prescribed treatment for gonorrhea. Because the disease caused by penicillinase-producing gonococci is clinically indistinguishable from uncomplicated gonorrhea, its spread in a community has serious implications for local health departments. To identify PPNG as the cause of a patient's infection, additional specific laboratory studies are necessary. More personnel time is required to recall patients for retreatment, and the drugs used to treat PPNG are five to ten times more costly than penicillin. In all likelihood, even with adequate resources available, the program's effectiveness would never approach 100%. Gonorrhea cultures have limitations imposed by sample collection, medium, and transport[11]; furthermore, not all infected patients return for treatment.

Once PPNG-caused gonorrhea exceeds an endemic level of 3% of all gonorrhea cases in a community, control is extremely difficult even with extraordinary measures. For example, the disease has continued uncontrolled in Florida despite a massive expenditure of federal manpower.[12] In Florida, PPNG now causes 7% of all gonorrhea cases reported there, and the proportion in some counties is as high as 50%.[13]

While the California Department of Health Services' 1987 PPNG treatment and control program was clearly a success, California's PPNG problem is by no means controlled. Importation of PPNG into California by both interstate and international routes continues and is most notable in Los Angeles and San Diego counties. Despite an intense effort during the past year, San Diego County has been unable to reduce the number of newly occurring cases of PPNG gonorrhea. Even more disturbing are recent reports from Los Angeles County of an inexplicable increase in the number of cases diagnosed since April 1988 that may indicate the establishment of a hyperendemic focus. Recognizing these trends, the CDHS makes the following recommendations.

Maintenance of Effort

- As long as PPNG accounts for 1% or more of all reported gonorrhea cases, epidemiologic and empiric treatment with ceftriaxone (or possibly spectinomycin) should continue.
- Each case should be aggressively investigated and epidemiologically managed and should include "clustering" techniques carried out by trained personnel.

Index of Suspicion

- Persons having cultures positive for gonorrhea or presenting with its symptoms should be carefully questioned about sexual contact with prostitutes and recent travel. Immediate treatment with ceftriaxone, preferably, or spectinomycin should be given to anyone who has recently traveled to areas where PPNG is hyperendemic. (The list of areas published monthly by the CDHS sexually transmitted disease section has consistently included Miami, New York City, and the Philippines.)
- Periodic alerts or status reports regarding the incidence and trends of PPNG infection at the state and community levels should be promulgated by public health officials for health care practitioners. At the very least, current morbidity trends and an updated list of hyperendemic areas should be provided.

Surveillance

- As long as PPNG accounts for 1% or more of reported gonococcal cases, laboratory testing of all gonococcal organisms for β-lactamase production should be done. In addition to PPNG surveillance, tetracycline-resistant *N gonorrhoeae* and chromosomally mediated and other resistant strains of gonorrhea should be monitored. Under grants from the Centers for Disease Control, California has established sentinel sites in three locations to routinely test antibiotic sensitivities in STD clinic patients with positive gonorrhea cultures. The 1987 sample indicated the presence of penicillinase-producing (1.8%), tetracycline-resistant (1.4%), and chromosomally mediated resistant organisms from the California sentinel sites (J. M. Zenilman, MD, Centers for Disease Control, written communication, January 1989).

Administration

- Local public health officials, especially those whose jurisdictions have had PPNG gonorrhea outbreaks in the past, should establish contingency plans so that such outbreaks can be managed as expeditiously as possible when they occur.

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Estrogen Replacement Therapy

THE MAJOR REASON for hospital stays, and indeed for death, for women above the age of 55 has nothing to do with the skeleton but is primarily due to ischemic heart disease. Women who have been treated with estrogen have a protection against ischemic heart disease, maybe even against stroke, which is of the magnitude of 35% to 40%. It could turn out that the most powerful thing a physician could do to protect a woman patient against heart disease after the age of menopause would be to place her on estrogen. The decision, therefore, as to whether a patient should or should not receive estrogen therapy really should be based on estimates of cardiovascular risk protection balanced by other potential toxicities that one might encounter, rather than on specific skeletal indications. Certainly, there is a need to protect the uterus against endometrial carcinoma. We have ways now—with the cycling, with progestins, and also with the use of continuous low-dose progestin on a continuous basis—to protect the uterus from endometrial hyperplasia, which is thought to be the precursor lesion to endometrial carcinoma.

—ROBERT MARCUS, MD

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Clinical Review

Psychotropic Medication Use During Pregnancy

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Women can have severe and at times life-threatening psychiatric illness during pregnancy. When nonpharmacologic interventions have been attempted and are insufficient, psychotropic medication use is often necessary. The available data on prescription neuroleptic drugs suggest that with the proper selection, use, and supervision, they can be used during pregnancy. The same cannot be said for lithium carbonate or most antidepressants owing to the risks of teratogenicity and toxicity to the fetus. It is prudent to avoid all medication use, if possible, during the first trimester, but deciding how and when to institute treatment depends on an assessment of the risks associated both with the drug and with the untreated illness.

(Guze BH, Guze PA: Psychotropic medication use during pregnancy. West J Med 1989 Sep; 151:296-298)

Those who treat pregnant women are, under most circumstances, cautious in their use of prescribed medications. On occasion, however, a woman taking psychotropic medication will discover that she has become pregnant. At this time she may ask her physician for advice concerning the relative risk to her unborn child. A patient's concern may include both the risk from previous exposure and the possible risk to the fetus from continued exposure.

In addition, when a serious mental disorder arises in a pregnant patient and nonbiologic methods such as individual, couple, or family psychotherapy, social casework, or admittance to hospital have been exhausted, it is often necessary to consider pharmacologic methods of treatment. If the risks associated with using psychotropic drugs are outweighed by the anticipated benefits and if the risk of inadequately treated disease outweighs that associated with a potentially useful medication, then most prudent physicians will opt to treat the disease. The dilemma for clinicians, however, is that no psychotropic drug has been proved safe for use during pregnancy and all carry warnings from the Food and Drug Administration.

Before prescribing a drug during pregnancy, many factors should be considered, including the effects of the drug during labor, the withdrawal effects on the newborn, if any, and the possibility that the medication will cause some form of congenital malformation. In addition, many consider it prudent to consult with a specialist in psychopharmacology before administering these drugs to pregnant women.

In this review we examine the risks to infants of in utero exposure, congenital malformation, and the possible postpartum effects of the use of lithium carbonate, antidepressants, and antipsychotic drugs.

Lithium Carbonate

Concerns about the use of lithium carbonate can be divided into the following areas: the metabolism of lithium during pregnancy, fetal lithium exposure, teratogenic effects, toxic reactions in the newborn, and breast-feeding.

Both the glomerular filtration rate and the effective renal plasma flow increase during pregnancy to approximately 45% above pregestational rates.[1] During this time, the plasma volume increases by about 50%. Renal lithium clearance increases in parallel with the increase in the glomerular filtration rate during pregnancy, and it may be necessary to progressively increase the intake of lithium to maintain a steady serum lithium concentration. During the postpartum period, a corresponding reduction in the amount of lithium administered is necessary to avoid possible toxic levels.[2,3]

It is important to tailor the dosage to each woman's needs. This is most accurately accomplished by using the minimum effective dose and frequent clinical and laboratory evaluations to ensure the maintenance of therapeutic lithium serum levels. To minimize the risk of toxic effects to the newborn and the mother, some physicians advocate discontinuing lithium therapy immediately before delivery.[4] It can be restarted, if indicated, as the mother stabilizes in the postpartum period.

Fetal blood is presumed to have the same serum concentrations of lithium as are found in the maternal blood.[5,6] There have been reports, however, of lithium toxicity in newborns when the maternal serum levels are below, within, or above the adult therapeutic range at the time of delivery. Symptoms in the infant are nonspecific and usually remit with supportive care.[2] Symptoms of neonatal lithium intoxication include cyanosis, jaundice, hypothermia, lethargy, hypotonia, a poor suck reflex, poor respiratory effort, an absent Moro's reflex, low Apgar scores, and altered thyroid and cardiac function that may take as long as ten days to resolve.[5,7,8(pp57-59)] Other reports have included nephrogenic diabetes insipidus, functional tricuspid regurgitation, congestive heart failure, and atrial flutter.[9-11]

Thyroid effects have also been reported in children born after in utero lithium exposure. Schou and co-workers described one child born with a large goiter that regressed spontaneously and another who was born with reversible hypothyroidism.[12]

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There is no clear evidence to establish lithium's role as a "behavioral teratogen." When children with in utero exposure to lithium were compared at follow-up with sibling controls, there was no significantly increased incidence of physical or mental anomalies in the children with exposure to lithium.[13] Conclusions were based only on the mothers' subjective assessments of their children, however, and not on the results of a physical examination or psychological testing.

The teratogenic effects of lithium are well documented in invertebrate and nonmammalian species.[14] Findings have included head and neck abnormalities, a disruption in the central nervous system development, and abnormal tissue differentiation. In many animal cases, however, serum concentrations exceeded those used in humans.

A "lithium baby register" was established in 1969 to collect information about the effects of lithium on in utero development.[15] By 1978 a high frequency of congenital malformations had been reported.[16] This may represent the tendency of such a method of data collection to overestimate the frequency of problems because clinicians are more likely to report a case in which there have been complications. Of 217 reported cases of exposure to lithium during at least the first trimester, 25 infants were born with congenital anomalies. Of the 25 infants, 18 had cardiovascular malformations, 6 of which involved Ebstein's anomaly of the tricuspid valve, atrial septum, and right ventricle. Based on these data, lithium has been suggested to be a cardiovascular teratogen.[5,17] Although the absolute incidence of malformations reported in the register is no higher than what is found in the general population, the register's data suggest that lithium not be used during the first trimester unless it is absolutely essential.[18]

Breast-feeding is complicated by the fact that the concentration of lithium in breast milk is about 50% of that in a mother's serum.[2] Lithium ingestion during breast-feeding is discouraged because of the concern for the development of toxic effects if there are fluid and electrolyte alterations in the infant, such as dehydration, and because the effect on an infant of ingestion by its mother of subtherapeutic levels of lithium is unknown. The decision to breast-feed should be undertaken only after a fully informed discussion between the parents and the physician. For some parents, the immunologic and psychological advantages of breast-feeding may outweigh the possible risks of lithium therapy.[7]

With the inability to predict exactly the risk associated with lithium use during pregnancy, only general guidelines are available. If lithium therapy is indicated, then the lowest serum levels possible that will provide adequate behavioral improvement should be used, and the total dose should be spread throughout the day, with each individual dose as low as possible.[5] Schou and Goldfield recommend additional guidelines for pregnant women on lithium therapy.[19] Its use should be discontinued for at least a month before pregnancy is attempted. If possible, a patient should be maintained free of lithium throughout the pregnancy. Lithium therapy should be reinstated only when the risk of relapse appears to exceed the possible morbidity of drug use. It should be discontinued, if possible, if a patient becomes pregnant. The woman should be told that many normal infants have been born to mothers taking lithium while pregnant. In addition, it is now possible to follow infant development in utero with such imaging procedures as ultrasonography to monitor the possible development of anatomic congenital anomalies.

Pregnant women are at risk for the same spectrum of adverse reactions as other patients—endocrine, renal, gastrointestinal, neurologic—but the physiologic changes of pregnancy may increase the relative risk.[20]

Antidepressants

Although direct proof of their teratogenicity is lacking, the use of cyclic antidepressant drugs has been associated with an increased risk of birth defects.[7,8,21,22] The results of studies in animals suggest that these agents can act as teratogens.[23] Although the ability of at least imipramine hydrochloride and desipramine hydrochloride to cross the placenta has been shown in both humans and animals,[24,25] in a study of 19 women taking imipramine and 28 women receiving amitriptyline hydrochloride during the first trimester of pregnancy, there was no evidence of congenital malformations.[26] In another study of 15,000 births, there was no evidence of gross congenital abnormalities in infants born to women who received tricyclic antidepressants during the first trimester.[27] From data contained in a register of 2,784 cases of birth defects matched to an equal number of control subjects, the teratogenic potential was estimated to be fairly low even with exposure during the first trimester.[28]

There does appear to be a greater consensus, however, that in the immediate postpartum period, a newborn can show the effects of antidepressants received in utero. There are reports of infants showing signs of respiratory distress, urinary retention, myoclonus, tachycardia, and heart failure.[8,22] Some of these infants have later shown signs of withdrawal.

The use of monoamine oxidase inhibitors should be avoided for several reasons. The possibility of a hypertensive reaction leading to severe vascular difficulties for both the mother and the fetus has been a common concern.[8] In addition, monoamine oxidase inhibitors have been shown to be teratogenic in animals.[29]

Antipsychotic Drugs

Phenothiazine and thioxanthene derivatives have been shown to cross the placenta.[30,31] Most reviews of the effects of neuroleptic drugs have not found a statistically increased incidence of structural birth defects in those infants with in utero exposure. A retrospective examination of 100 women receiving haloperidol while pregnant revealed no notable effect on the sex ratio of offspring, birth weight, intrauterine or neonatal survival, fecundity, or duration of gestation compared with controls.[32] In a review of 341 cases of intrauterine exposure to trifluoperazine hydrochloride, there was no increased incidence of congenital anomalies compared with the general population.[33]

In a prospective study of 12,764 women and their offspring receiving exposure to phenothiazines in the first trimester, a statistically significant increase was found in the incidence of major congenital anomalies when the exposure was to phenothiazine derivatives with a 3-carbon aliphatic side chain: chlorpromazine, methotrimeprazine, trimeprazine tartrate, and oxomemazine.[34] These side effects included malformations of the central nervous, cardiovascular, digestive, musculoskeletal, and genitourinary tract systems. There was a high incidence of microcephaly, ventricular septal defect, cleft lip, hypospadias, polydactyly, and syndactyly. This was not observed with the use of promethazine hydrochloride or the piperidine and piperazine antipsychotic

drugs. Of the drugs suggested by this report to have a deleterious effect, only chlorpromazine is used as an antipsychotic in the United States.

Contradictory findings were reported in a study of 19,952 women treated with phenothiazines during their first trimester. There was no significant increase in the incidence of severe congenital anomaly and perinatal death for the group receiving exposure versus controls.[35]

Toxic effects have been reported in newborns, including restlessness, abnormal movements, hypertonia, and an extrapyramidal syndrome that includes tremor, hypertonia, weakness, and poor sucking and sluggish primitive reflexes.[36-39] This syndrome may be familial and is most likely dose-dependent.[8] Extrapyramidal symptoms in the newborn are reported to persist for as long as six months.[39]

Nonphenothiazine or nonbutyrophenone antipsychotic drugs such as thiothixene, molindone hydrochloride, or loxapine hydrochloride have not been investigated sufficiently to accurately report the incidence of fetal abnormalities associated with their use during pregnancy.

As a generalization about the use of antipsychotic drugs during pregnancy, some authorities have suggested that it is best to avoid their use during the first trimester and to consider their use during subsequent trimesters only under urgent circumstances.[7,8]

Benzodiazepines

Early reports evaluating the effects of benzodiazepine exposure on fetal formation described an increased incidence of malformations such as cleft lip or palate following early fetal exposure.[40] More recent studies have failed to confirm this finding, however.[41] A survey of 19,000 pregnant women also failed to find an increase in the incidence of congenital malformations in babies with exposure to benzodiazepines.[42]

A neonatal abstinence syndrome has been reported in neonates born to mothers who ingested benzodiazepines in the last trimester of pregnancy.[43] It consists of tremor, increased sucking, irritability, and hypertonicity. Depression of the neonatal central nervous system may occur following the administration of benzodiazepines during labor.[44] Its manifestations include hypothermia, apnea, and an impaired suck reflex.

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Medical Progress

Transcatheter Therapy for Malignant Neoplasms

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Interventional radiology has developed into a subspecialty with application in the treatment and palliation of patients with advanced malignant diseases. A directed catheter delivers high concentrations of chemotherapy directly into the tumor bed. Embolic particles may be injected to stop hemorrhage or to occlude the blood supply of a cancer, resulting in pain relief or tumor shrinkage. These techniques can be incorporated into a multidisciplinary approach to cancer.

(Coldwell DM, Mortimer JE: Transcatheter therapy for malignant neoplasms. West J Med 1989 Sep; 151:299-303)

Advances in chemotherapy have resulted in a cure for patients with such widespread cancers as Hodgkin's and non-Hodgkin's lymphomas, testicular cancer, and acute lymphocytic and nonlymphocytic leukemia. Most systemic malignant neoplasms, however, are treated with a palliative intent. Optimal therapy for such patients uses the combined expertise of the surgical, medical, and radiation oncologists. Prolonging a high quality of life is the goal that must balance the toxic effects to the tumor with those to normal tissues. The emergence of interventional radiology as a subspecialty has resulted in a refining of techniques that allow a percutaneously placed catheter to replace more morbid surgical procedures. Interventional radiologists may be helpful in controlling localized bleeding, the infarction of tumors, and in the regional administration of chemotherapy. We summarize some of these techniques and their applications.

Hemorrhage

Hemorrhage may be a complication of tumor growth or may result from tumor regression following irradiation or chemotherapy for disease that invaded the vessel wall. Interventional radiologists are called on to do the definitive procedure to document the sites of bleeding. A catheter may be left in place for infusing vasopressin in an effort to control the bleeding. Benign sources of bleeding may be controlled with regional infusions of vasopressin as normal vessels constrict in response to this agent. Vessels in malignant tissues do not respond predictably to vasopressin. Therefore, a superselective embolization of the offending artery using absorbable gelatin sponge (Gelfoam), polyvinyl alcohol foam particulate emboli, or sclerosing agents is done to control hemorrhage due to tumor.[1,2] Embolization may be the noninvasive treatment of choice for hemorrhage caused by tumor. Success with such an intervention has set the stage for using the skills of interventional radiologists in drug delivery and the occlusion of tumor vessels to control bleeding preoperatively or as a tumoricidal technique, as indicated in Figure 1.

Angiographic Embolization

Liver metastases are a major source of morbidity and mortality for a number of cancers but especially those of the gastrointestinal tract. Of patients dying of colon cancer, 80% die of hepatic failure.[3] Surgeons were the first to focus on palliating hepatic metastases by taking advantage of the dual blood supply to that organ. The normal liver derives 80% of its blood supply from the portal vein and 20% from the hepatic artery. Metastatic lesions, however, derive at least 80% of their blood supply from the hepatic artery.[4] Surgically ligating the hepatic artery could therefore produce tumor ischemia without compromising the blood supply to the normal liver. Ligation of this large vessel, however, is less precise than ligation of the specific blood vessels supplying the metastases. Further limitations of the procedure include the need for an abdominal operation and the rapid development of collateral blood vessels despite an initial ischemia. Clearly the benefit of ligation is of short duration.[5]

Interventional radiologists can gain access to the arterial system through a femoral approach using the Seldinger technique. Under fluoroscopic guidance a selective arteriogram is done and the catheter is placed directly into the vessels supplying the hepatic metastases. The hepatic artery can be embolized by injecting materials that occlude the arterial system at any desired level, from the largest artery to the capillary bed. Both absorbable substances (blood clots, muscle, Gelfoam, and Avitene) and nonabsorbable materials (Ivalon sponge, silicone microspheres, steel coils, and sclerosing agents such as alcohol) have been used for this purpose. The occlusive effect of particles is more predictable than that of solutions. Larger embolic particles embolize larger vessels. Collateral vessels form rapidly after a large vessel is occluded—as exemplified by the experience with the surgical ligation of the hepatic artery. To create tumor ischemia and slow the formation of large-caliber collaterals, the smaller diameter embolic particles are preferred. Gelfoam powder (40 to 60 microns), polyvinyl alcohol particles (149 to 500 microns), and cross-linked collagen particles (60 to 80 microns) are used most often. Some substances are resorbed rapidly by the body, thereby limiting the benefit of embolization. Gelfoam and cross-linked collagen particles are resorbed after embolization. We generally use polyvinyl alcohol foam particles, which are not resorbed by the body.[6,7]

After vascular access is gained, a "mapping" arteriogram is done to delineate all the vessels feeding the tumor and to identify the vascular anatomy because only 55% of the

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population has "normal" celiac arterial anatomy. A second angiogram is done after a superselective catheterization of the tumor to show the precise distribution of the vessel to be embolized. The embolic particles are slowly injected through the catheter until vascular stasis occurs. Although not generally done, stasis or obliteration of all approachable feeding vessels can be confirmed by withdrawing the catheter to the next most proximal bifurcation before contrast is injected so as not to dislodge the embolic particles. In experienced hands this procedure takes from one to three hours to do and uses 200 to 300 ml of contrast material. It is recommended that the volume of contrast be kept below 4 ml per kg of body weight. It is not advisable to embolize all tumors in all lobes of the liver due to the severity of the postembolization syndrome. Tumors in the distribution of the right and left hepatic arteries are customarily embolized in two procedures separated by three to four weeks. Often a third procedure is done three weeks later to ensure vascular stasis both in the distribution of the hepatic arteries and in collateral circulation.

Some degree of a "postembolization" syndrome develops in all of these patients. The syndrome is a result of infarction of the tumor and tumor necrosis and manifests as nausea, vomiting, fever, pain, leukocytosis, and rapid elevations of indices of liver function. The nausea and vomiting are controlled by routine measures. The hepatic pain may be severe enough to require continuous infusions of morphine sulfate, and the temperature may spike as high as 40°C.[8] Recent work has shown that a celiac plexus block will alleviate most of the pain for the duration of the postembolization syndrome.[9] Serum levels of aminotransferases, alkaline phosphatase, lactic dehydrogenase, and bilirubin rise rapidly. The serum aspartate aminotransferase level is a good indicator of the clinical syndrome, peaking after three to five days. We have routinely kept patients in hospital until their aminotransferase levels have peaked.[10]

Hepatic necrosis, the most severe complication of embolization, may be avoided by ensuring that the portal vein is patent on the mapping arteriogram. The hepatorenal syndrome is a rare complication of this procedure and may be avoided by a careful patient selection. Patients risk having this syndrome develop if any three of the following are present: a total bilirubin value of more than 34 μmol per liter (2.0 mg per dl), an alkaline phosphatase level of greater than 450 U per liter, an aspartate aminotransferase value of greater than 200 U per liter, and greater than 70% of the hepatic parenchyma replaced by tumor (C. Charnsangavej, MD, oral communication, August 1988). The unintended necrosis of tissue due to misplaced embolic particles is usually a function of inexperience.[11] Using cross-linked collagen particles that are of a smaller diameter than polyvinyl alcohol, sepsis has been reported.[12] Of 226 patients treated with a cisplatin and mitomycin chemoembolization, 1 died of *Clostridium difficile* sepsis. This is rare with polyvinyl alcohol.[13]

Tumors for which hepatic arterial embolization (HAE) may be beneficial are those that are not resectable but are confined to the liver. Historically, secretory endocrine tumors have been palliated using cyproheptadine hydrochloride or, more recently, a somatostatin analogue for the control of symptoms. Although these tumors are sensitive to chemotherapy agents such as streptozocin, fluorouracil, and dacarbazine, objective tumor regression and symptomatic relief take weeks to months. Because hepatic arterial embolization is associated with an immediate resolution of hormonally mediated syndromes, its use is advocated as first-line therapy in institutions with the capability of doing it.[14,15] The effect of HAE in carcinoid tumors is shown in Figure 2.

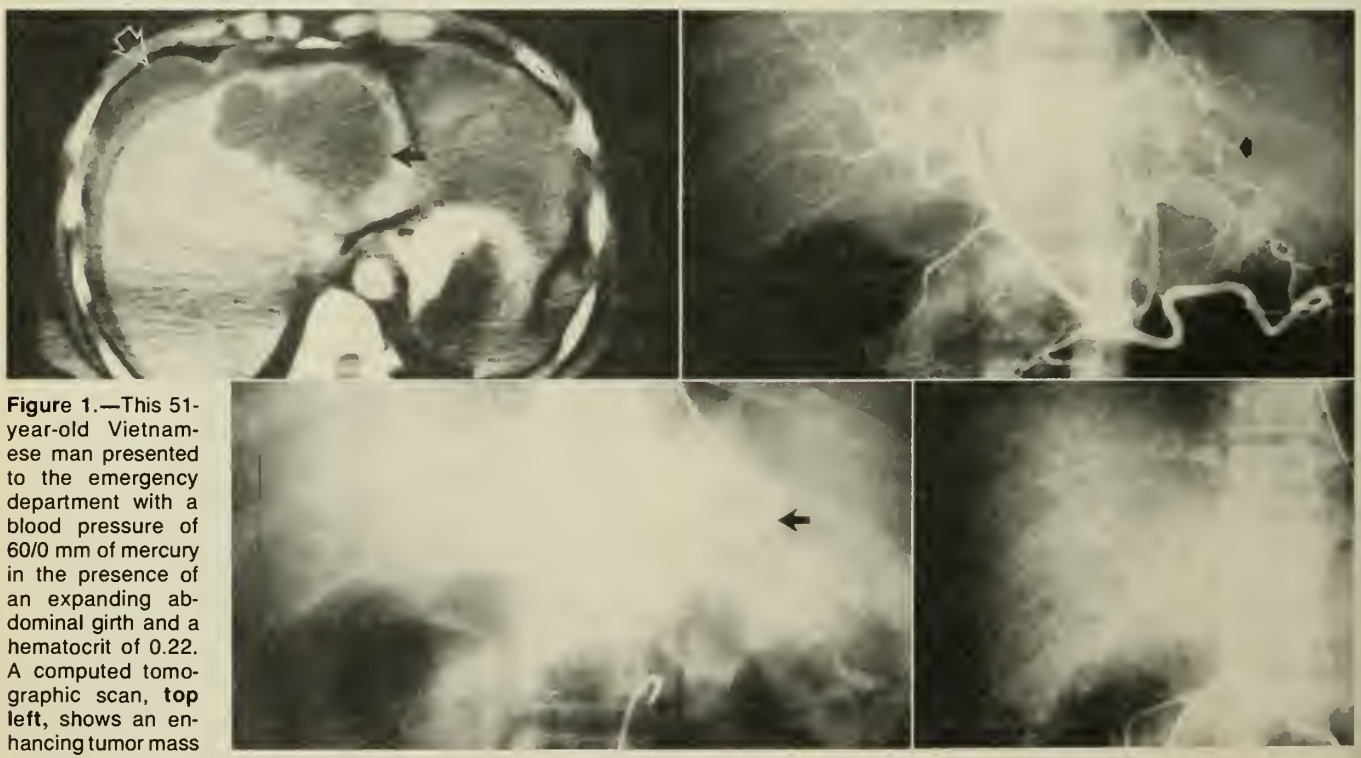

Figure 1.—This 51-year-old Vietnamese man presented to the emergency department with a blood pressure of 60/0 mm of mercury in the presence of an expanding abdominal girth and a hematocrit of 0.22. A computed tomographic scan, **top left**, shows an enhancing tumor mass **(arrow)** in the left lobe of the liver with fresh blood in the peritoneum **(open arrow)**. **Top right**, a celiac arteriogram shows the hypervascular hepatocellular cancer **(arrow)**, and, **bottom left**, a later film confirms active bleeding as contrast spilling into the peritoneal cavity **(arrow)**. A superselective embolization with polyvinyl alcohol was done through the left hepatic artery. **Bottom right**, A subsequent proper hepatic arteriogram confirms occlusion of the bleeding vessels.

Primary hepatocellular cancers are also amenable to hepatic arterial embolization. A prospective randomized trial has compared repeated HAE with a single HAE procedure combined with fluorouracil chemotherapy, and with fluorouracil chemotherapy alone. Tumor regression was measured by ultrasound imaging. A significantly higher response rate, 43%, occurred in the HAE group compared with 14% treated with a single HAE and fluorouracil, and with 0% treated with chemotherapy only. Likewise, an overall survival advantage was seen for the patients treated by repeated hepatic arterial embolization.[16]

Encouraging results have occurred in patients with liver metastases from primary ocular melanoma where complete tumor regression was observed on a computed tomographic scan following serial hepatic arterial embolizations.[17] Conventional wisdom has held that only hypervascular lesions, such as tumors of amine precursor uptake and decarboxylation cells, hepatomas, sarcomas, and melanomas, would benefit from HAE. In our experience with colorectal cancers, usually a hypovascular tumor, symptomatic relief of pain can be achieved with this therapy.[18] Further studies are ongoing.

The surgical resection of hypervascular tumors is associated with a higher morbidity—from blood loss and longer operating times. The technique of tumor embolization has been used in the preoperative setting to facilitate resection. The initial studies using preoperative embolization in renal cell cancer suggested a decreased incidence of distant metastases in addition to decreasing blood loss, as seen in Figure 3. Subsequently a prospective randomized trial failed to confirm the decreased incidence of distant metastases but did support a decreased surgical morbidity.[19] Renal embolizations have also been used to control pain, hematuria, hypertension, and mass effects as well as the primary tumor in patients with a single functioning kidney. The use of tumor embolization before the resection of other primary tumors (sarcomas) and of hypervascular metastases is being studied.

Arterial Chemotherapy

In theory, intra-arterial chemotherapy may have advantages over intravenous chemotherapy. In disease localized to a single arterial distribution, this route allows a high concentration of drug to be extracted by the tumor (first-pass effect) with a minimum of systemic toxicity. Tumors in which this has been tested include colorectal cancer with liver metastases, head and neck cancers, brain tumors, and sarcomas. Historically, a surgical procedure was required for implanting vascular access devices in the hepatic artery or to gain temporary access to other arteries. A transfemoral approach allows a radiologist to cannulate most arteries. In most instances the catheter remains in place for the chemotherapeutic administration, 30 minutes to 4 days, of infusional therapy. The patient is discharged without the need to care for an indwelling access device. Both the surgically implantable devices and intermittent transfemoral catheterizations allow for adequate drug delivery. In randomized trials comparing intravenous with hepatic arterial administration of fluorouracil and floxuridine, response rates appear to be superior when the drug is given arterially, without improving the overall survival.[20,21]

Cisplatin is an agent for which there is a major theoretic advantage to using the arterial route. Because free platinum, the active ingredient of cisplatin, binds rapidly to serum

Figure 2.—A proper hepatic arteriogram shows the hypervascular metastases **(top)** and vascular blush **(middle)** in a 60-year-old woman with recurrent carcinoid tumor. One month after the tumor within the distribution of the right hepatic artery was embolized, a computed tomographic scan **(bottom)** reveals necrotic tumor in that portion of the liver **(arrow)**.

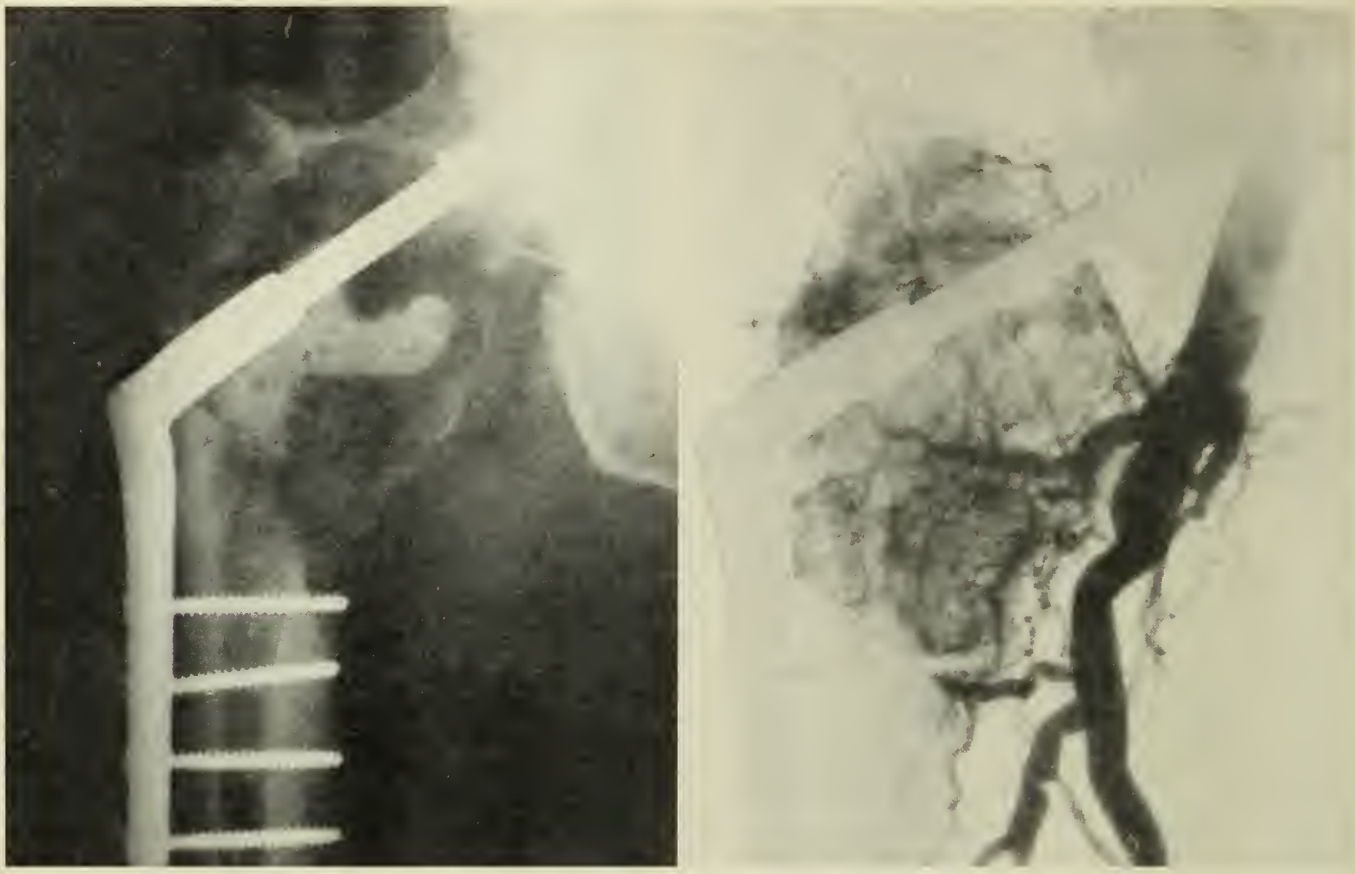

Figure 3.—Embolization of this hypervascular metastasis **(left** and **right)** to the femoral neck from a renal cell cancer was done before a total hip replacement. Blood loss was kept to a minimum.

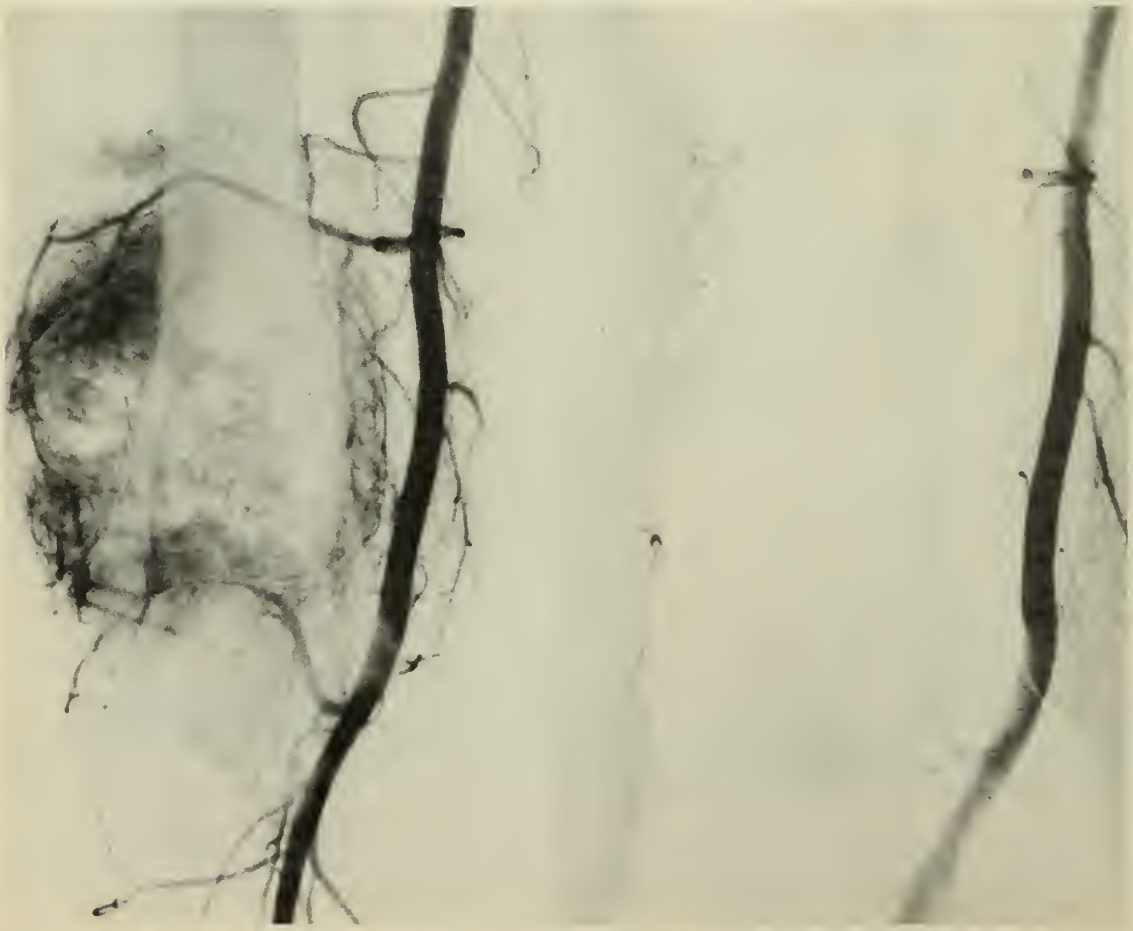

Figure 4.—A 17-year-old man with a hypervascular osseous sarcoma **(left)** was treated with intra-arterial chemotherapy before an operation. **Right,** An arteriogram following four cycles of chemotherapy suggests tumor regression as loss of the tumor vascularity. The surgical specimen contained only necrotic tumor.

proteins, arterial administration may provide a high concentration of the active component directly to the tumor site.[22] Phase II studies of arterial cisplatin in head and neck cancers, sarcomas, and brain tumors suggest a higher response rate than seen with comparable doses given intravenously.[23-25] Randomized trials, however, are still lacking. Figure 4 illustrates an osseous sarcoma before and after regional chemotherapy.

Chemoembolization

Chemotherapy may be combined with embolization to create high concentrations of regional chemotherapy. A chemotherapeutic agent such as cisplatin has been combined with the embolic particles, thus "sandwiching" chemotherapy in the immediate tumor region. This allows a slow leeching of drug into the tumor bed. Although this technique is entirely investigational, the initial results are promising.[12]

Interventional radiologists have developed a role in the multidisciplinary management of cancer. Percutaneous vascular access has obviated the need for an operation in selected instances for the control of bleeding or to gain vascular access for regional chemotherapy. Preoperative embolization of vascular tumors can decrease surgical morbidity. Serial hepatic arterial embolization of metastases may be considered first-line therapy for controlling symptoms due to hormones secreted by tumors of amine precursor uptake and decarboxylation such as carcinoids. The results of hepatic arterial embolization in primary hepatomas are encouraging, and the therapy is under investigation on other tumor types.

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Medical Staff Conference

The Clinical Challenges of Myocardial Infarction in the Elderly

Discussant
HARLAN M. KRUMHOLZ, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *However they are defined, the elderly are clearly becoming an increasingly important group in the population physicians care for. In this conference Harlan Krumholz, MD, reviews the particular challenge of the diagnosis and treatment of only one of the many diseases more common in the elderly, myocardial infarction. His remarks are important not only for their relevance to this important disease but also for their definition and illustration of the issues involved in treating elderly patients with any serious condition. Dr Krumholz has served with distinction as the Medical Chief Resident at the University of California, San Francisco (UCSF), and will next year pursue further his interest in myocardial infarction as a fellow in cardiology at Harvard Medical School and Beth Israel Hospital in Boston.*

HARLAN M. KRUMHOLZ, MD†: Physicians are caring for a rapidly growing segment of the population, the elderly, with little clinical information. Heart disease, the leading health problem in the elderly, is the most blatant example of this problem. The bulk of the understanding of ischemic heart disease is gleaned from studies that focused primarily on middle-aged populations. Meanwhile, the practice of medicine is increasingly directed toward an older group.

In this review I explore what is known about the elderly and myocardial infarction. The review is organized around five interrogatives: who, why, how, what, and when. I discuss who the elderly are, why heart disease and myocardial infarction in the elderly deserve our attention, how the elderly present with myocardial infarction, what evidence is available about therapies in the elderly, and when these therapies ought to be applied.

Who Are the Elderly?

Any attempt to define an elderly population is fraught with difficulty. What is that evanescent boundary that separates middle age from old age? It is far easier to refer abstractly to a group of "older" Americans than it is to define the group more precisely with firm dividing lines.

In a culture that rejects old age and embraces youth, the task of defining the elderly is particularly delicate and should be undertaken with care. Designating a group as "elderly" is widely regarded as a value judgment rather than an attempt to define a group of interest. In our culture everyone wants to live a long time, but no one wants to grow old.

Aging is a continuous process, and establishing a border across which a person passes from "middle age" to "old age" is artificial. Physiologic aging occurs at a varying rate within the population, and, thus, groups of adults defined by their chronologic age show great heterogeneity. Chronologic age provides an imperfect marker for physiologic age.

The younger the boundary for the elderly, the greater the heterogeneity of the defined group. In 1935, with the passage of the Social Security Act, age 65 was embedded in our national consciousness as the beginning of old age. Today, however, age 65 is considered relatively young. As a result of improvements in infant mortality and childhood death, about one in eight Americans today is 65 years or older, or roughly 30 million people. This compares with one in ten Americans aged 65 years or older at the turn of the century. The average life expectancy today for a person aged 65 is almost 17 years.[1]

Americans over 65, therefore, are not merely clustered between the ages of 65 and 75. Currently more than 40% of the population 65 years and older is aged 75 or more.[1] This group of senior citizens constitutes a rapidly growing portion of our population. For instance, the number of centenarians in the United States increased from 15,000 to 25,000 over the six years from 1980 to 1986.[1] As the "baby-boom" generation—those born between 1946 and 1964—reaches maturity, this number will increase even more dramatically. Given current projections, the number of people aged 85 and older will increase more than 700% between the years 1980 and 2050,[1] at a time when the rest of the population is expected to increase by only a third. Many people, therefore, now make the distinction between the young-old (65 to 74) and the old-old (75+). The focus of this discussion is on the older group.

The elderly are voracious consumers of health care. The 65 years and older group, representing 12% of the population, accounts for a third of the country's total personal

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ABBREVIATIONS USED IN TEXT

AIMS = APSAC Intervention Mortality Study
APSAC = anisoylated plasminogen streptokinase activator complex
ASSET = Anglo-Scandinavian Study of Early Thrombolysis
GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico
ISIS-2 = Second International Study of Infarct Survival
UCSF = University of California, San Francisco

health care expenditures. In 1985 this group accounted for 30% of the country's hospital discharges and 41% of the hospital days of care.[1] Meanwhile, the group 75 years and older, representing 5% of the population, was responsible for 16% of all hospital discharges and 22% of all hospital days.[1] The group 85 years and older, representing just 1% of the population, accounted for 4.4% of the hospital discharges and 6.5% of the hospital days.[1]

Physicians see these patients commonly. Aside from the frequent hospital admissions, the average person aged 75 years and older visits a physician more than ten times a year. Almost 90% of this group have seen a physician within the past year.[1] This ready access to physician and hospital services by the elderly is a tribute to our federal insurance system.

The elderly are a common sight at this medical center. In the period from January through April 1989, for instance, the UCSF Emergency Department saw 420 octogenarians, about 7% of the total emergency department visits. Meanwhile, almost 20% of the patients admitted to the coronary care unit are 75 years or older.

Why Heart Disease in the Elderly Deserves Attention

Heart disease is the most important cause of mortality, morbidity, and the consumption of resources in the elderly. In fact, the preponderance of all deaths from heart disease occurs in the 65 years and older group. Heart disease is very much a disease of the elderly.[2]

Despite recent declines, heart disease far exceeds stroke and cancer as a cause of death in the elderly and in the use of resources. In the group 75 to 84 years, heart disease is responsible for 43% of overall deaths (cancer causes 20% of the deaths in this age group). In the 85 years and older group, heart disease accounts for 48% of the deaths.[1]

The importance of heart disease in the elderly is not merely an artifact of the death certificate. It is the leading cause of physician visits, hospital days, and short-stay hospital days for the elderly. In 1985 this important health problem accounted for 10% of all physician visits and almost 20% of hospital days.[1] In our emergency department, of the 420 visits by octogenarians between January and April 1989, 20% were for heart disease. The great majority, 85%, of these patients were admitted to the hospital.

How the Elderly Present With Myocardial Infarction

Myocardial infarction can be a subtle diagnosis at any age. Information from the Framingham study suggests that at least a quarter of infarctions occur without being diagnosed by a physician. Although many of these are truly silent infarctions, at least half are characterized by atypical symptoms.[3]

Despite the common wisdom that myocardial infarction presents atypically in the elderly, the literature suggests that most elderly patients actually are seen for either chest pain or shortness of breath. A review of our own experience supports this finding. Among 43 octogenarians who suffered an acute myocardial infarction at UCSF in the 18 months between October 1986 and April 1988, 35 (more than 80%) presented with either chest pain or shortness of breath. Although some came to medical attention with other symptoms including nausea, confusion, dizziness, and syncope, they were few in number. In addition, we diagnosed myocardial infarctions in a few completely asymptomatic patients being evaluated for anemia.

In a recent study, atypical presentations in the elderly correlated best with poor performance on a modified mental state examination.[4] It may be that atypical presentations occur most often in persons unable to communicate their symptoms well.

Are many myocardial infarctions missed in the elderly? The Framingham data for patients 75 years or older are sparse. Although the older men appear to have more unrecognized infarctions, the difference from younger groups is insignificant.

In another study autopsies that revealed a recent myocardial infarction were reviewed.[5] The investigators discovered that the correct antemortem diagnosis was made in only 43% of the cases. Infarctions were missed more often in the older patients. In patients older than 60—mean age of 72.1 ± 8.3 years— the authors found that the correct diagnosis was made in only 38%. The number of atypical presentations was no greater in the older group, however, and did not account for the discrepancy, but the older group did have many other coexistent diseases.

Overall it appears that myocardial infarctions are more often undiagnosed in the elderly, but they, nonetheless, present typically. The high prevalence of heart disease in the elderly should alert all physicians to both typical and atypical symptoms in this age group. The presence of more than one disease can obscure the importance of symptoms, typical or atypical, related to heart disease.

What Therapies Are Effective in the Elderly?

In recent years medical science has made significant progress in the treatment of myocardial infarction. Most of the trials of the efficacy of various interventions, however, have focused on middle-aged patients. These trials have provided little information on the effect of therapy on patients 75 years and older.

Decisions about the treatment of myocardial infarction in the elderly are limited by inadequate information. The extrapolation of results from middle-aged patients may not apply to the elderly, a group with a shorter life span, more coexistent diseases, and perhaps a different physiology. Furthermore, survival benefits in patients with relatively short life expectancies may be less important than quality-of-life considerations.

Although there is a dearth of information about myocardial infarction in the elderly, physicians every day are faced with treatment decisions in patients aged 75 years and older. All patients admitted with a myocardial infarction, for whom treatment is appropriate, receive therapy directed at relieving pain, reducing myocardial oxygen uptake, and supporting the blood pressure, in addition to monitoring for arrhythmias. While these interventions remain the founda-

tion for treatment in all age groups, pharmacologic interventions in the elderly must be instituted with care. All the possible adverse effects of the medical armamentarium occur more frequently in the elderly. The use of medicines in the elderly poses an important challenge because of age-related changes in drug absorption, distribution, metabolism, and excretion. In addition, the elderly are more likely to be taking many drugs, leading to the problems of drug interactions, noncompliance, or confusion about the correct dose.

What about other interventions? Physicians can only proceed from a good knowledge of the information about the elderly that is currently available. In particular, do aspirin, thrombolytic therapy, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, and secondary prevention have a role in the treatment of myocardial infarction in patients 75 years or older?

Should Elderly Patients With Myocardial Infarction Receive Aspirin?

Aspirin, truly one of the wonder drugs, has an established role in the treatment of many cardiovascular diseases. Recently the Second International Study of Infarct Survival (ISIS-2) collaborative group showed that a regimen of 160 mg a day of aspirin, started within 24 hours of the onset of symptoms and continued for a month, was as effective as thrombolytic therapy in reducing mortality from acute myocardial infarction.[6] When used with thrombolytic therapy, the effect of the two agents was additive and produced an even greater survival benefit.

The ISIS-2 trial enrolled over 17,000 patients from more than 400 hospitals across Europe. Fortunately, they did not have an upper age limit. The use of aspirin reduced mortality in every age group (Figure 1). More than 3,000 patients older than 70 years were enrolled in the arm of the study comparing the use of placebo and aspirin. The use of aspirin reduced vascular mortality at five weeks from 22.3% to 17.6%. Aspirin administration should be a part of the treatment of every person, at any age, who presents with myocardial infarction and does not have a strong contraindication to taking the medicine.

Should Elderly Patients With Myocardial Infarction Receive Thrombolytic Therapy?

Thrombolytic agents offer physicians an effective way to limit, and in some cases abort, acute myocardial infarction. Four large trials—the Italian Group for the Study of Streptokinase in Myocardial Infarction (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico, GISSI),[7] the APSAC [anisoylated plasminogen streptokinase activator complex] Intervention Mortality Study (AIMS),[8] ISIS-2,[6] and the Anglo-Scandinavian Study of Early Thrombolysis (ASSET)[9]—have shown a reduction in mortality rates with the use of thrombolytic therapy in acute myocardial infarction (Figure 2). These trials have enrolled a varying number of elderly patients.

The GISSI study, published in 1986, did not have an age limitation. They randomly allocated almost 3,000 patients between the ages of 65 and 74 and more than 1,000 patients older than 75 years. In both groups streptokinase therapy reduced the mortality rate at 21 days, although neither result was statistically significant (Figure 3).

Published in 1988, the APSAC Intervention Mortality Study, a large, randomized, double-blind, placebo-controlled trial of the effect on survival of a single dose of anisoylated plasminogen streptokinase activator complex given within six hours of the start of an acute myocardial infarction, was open to patients aged 70 years or younger. Only 176 patients who were between 65 and 70 years old were enrolled. The intervention significantly reduced mortality in the patients 65 years and older from 30.2% to 12.2%. The benefit appeared greater in the older patients than in the younger ones (Figure 4).

The ISIS-2 trial also provided important information about the effectiveness of thrombolytic therapy in the elderly. The trial, published in 1988, enrolled more than 3,000 pa-

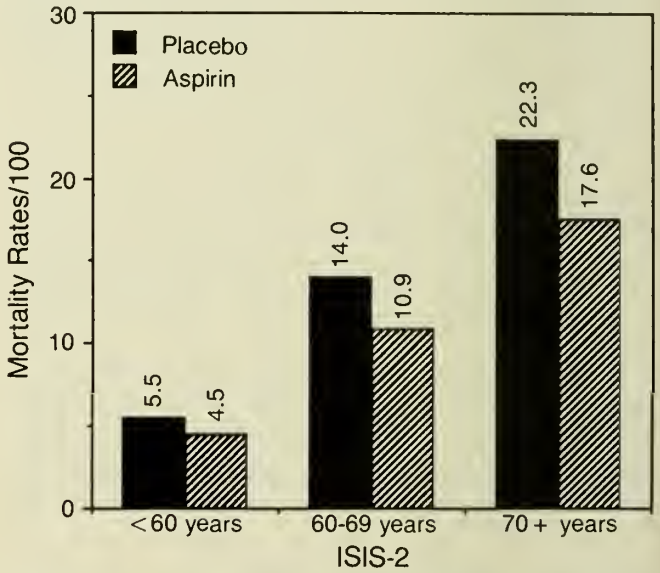

Figure 1.—The results shown in the graph reflect the mortality rates in the arm of the Second International Study of Infarct Survival (ISIS-2) that compared the use of aspirin with placebo. The results in each subgroup are statistically significant ($P<.05$) (adapted from the ISIS-2 study[6]).

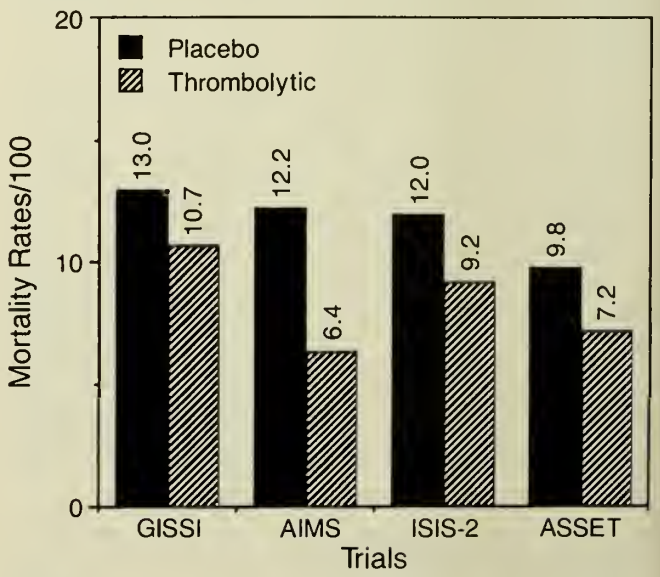

Figure 2.—The studies in the graph showed that thrombolytic therapy significantly reduced mortality from myocardial infarction (adapted from the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [GISSI],[7] the APSAC [anisoylated plasminogen streptokinase activator complex] Intervention Mortality Study [AIMS],[8] the Second International Study of Infarct Survival [ISIS-2],[6] and the Anglo-Scandinavian Study of Early Thrombolysis [ASSET][9] trials).

tients 70 years or older into the arm comparing the use of streptokinase and placebo. Administering streptokinase significantly reduced mortality from 21.6% to 18.2% (Figure 5). The effect of streptokinase was increased with the addition of aspirin, as the mortality rate was reduced from 23.8% to 15.8%.

The Anglo-Scandinavian Study of Early Thrombolysis, a double-blind, placebo-controlled trial of the effect of tissue plasminogen activator and heparin compared with heparin and placebo for the treatment of myocardial infarction, enrolled more than 1,500 people who were 66 to 75 years old. On a subgroup analysis, the older patients had the most impressive benefit from the treatment. The group 56 years and younger had a statistically insignificant reduction in mortality from 4.4% to 3.8%. Meanwhile, the group aged 66 to 75 years had a statistically significant reduction in mortality from 16.4% to 10.8% (Figure 6).

The studies, published in 1988, thus strongly suggest that thrombolytic agents have a role in treating the elderly. The two studies that had no age limit, GISSI and ISIS-2, both showed a benefit with thrombolytic therapy, although in the GISSI trial the difference was not statistically significant. The other trials provide firm support for thrombolytic therapy in persons as old as 70 years (AIMS) and 75 years (ASSET). Given these results, in the absence of a contraindication, age itself does not seem a legitimate reason to deprive a patient of the benefit of these agents.

Should Elderly Patients With Myocardial Infarction Have Percutaneous Transluminal Coronary Angioplasty?

The role of percutaneous transluminal coronary angioplasty in the treatment of myocardial infarction, in all age groups, is adjunctive.[10] This procedure, carried out in patients with acute myocardial infarction, provides no greater benefit than administering thrombolytic agents. Furthermore, recent studies show that it has no role immediately following thrombolytic therapy.[11] Only patients with a contraindication to thrombolytic therapy should be considered for coronary angioplasty as the primary therapeutic intervention.

In addition, there is a paucity of data about the use of percutaneous transluminal coronary angioplasty in the elderly. The little data that are available suggest that it holds no special benefit for this group, as success rates for the elderly are lower than in younger groups.[12] No controlled trials have been done in the elderly to guide physicians' approach.

Should Elderly Patients With Myocardial Infarction Have a Coronary Artery Bypass Graft?

In patients with acute myocardial infarction, there is no role for surgical treatment as a primary intervention. Patients with an infarction that progresses in a stuttering fashion are often considered for an operation, but there are

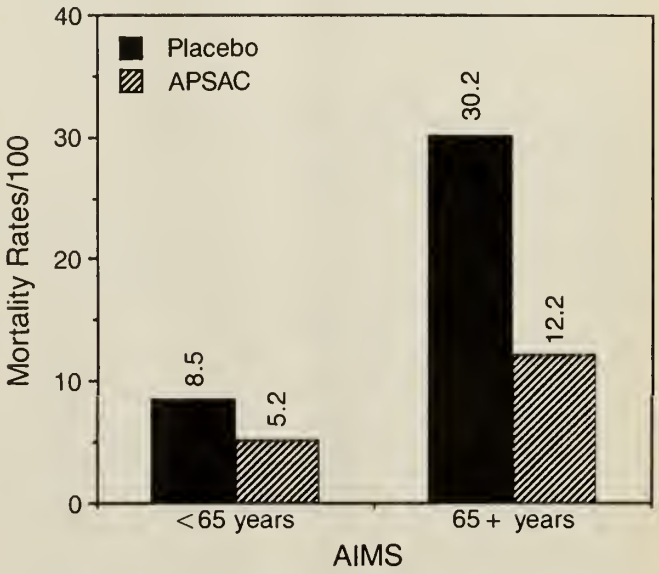

Figure 4.—The administration of anisoylated plasminogen streptokinase activator complex (APSAC) significantly reduced mortality in both age groups (adapted from the APSAC Intervention Mortality Study [AIMS][8]).

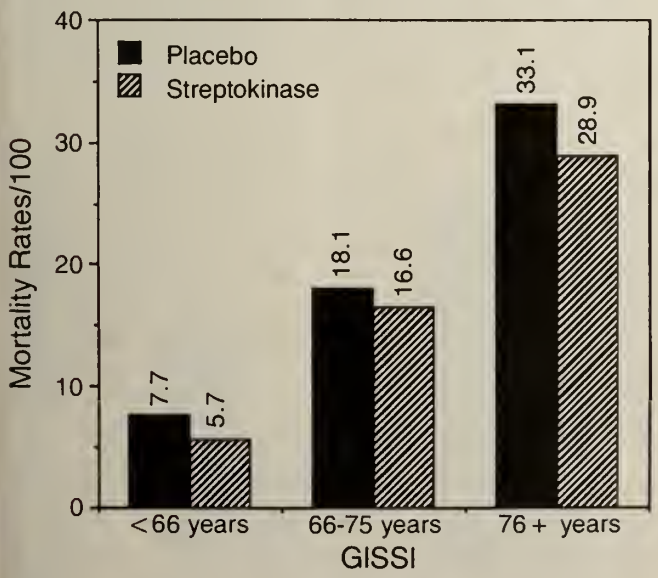

Figure 3.—Streptokinase therapy reduced mortality rates in all age groups, but the difference was significant only in the group aged 65 years and younger (adapted from the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [GISSI] trial[7]).

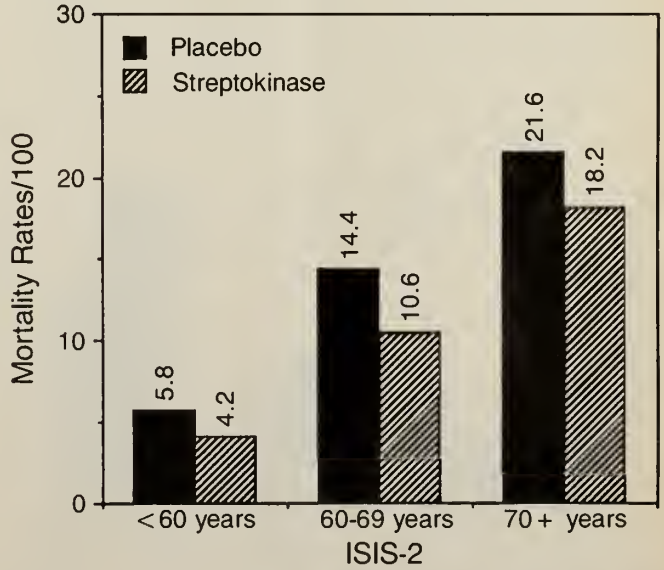

Figure 5.—Streptokinase therapy significantly reduced mortality rates in all age groups (adapted from the Second International Study of Infarct Survival [ISIS-2][6]).

no randomized trials, in any age group, to establish the benefit.

Patients who survive their myocardial infarction but who have residual coronary artery stenosis may also be considered for surgical intervention. Large clinical trials have identified groups of patients likely to have a survival benefit from an operation.[13] There are no such trials, however, for the elderly. Studies have shown that elderly patients have a higher surgical mortality than younger patients.[14-20]

Although an increasing number of patients 75 years and older are having coronary artery bypass grafts, the survival benefit to these patients is uncertain. Studies do not address whether patients who have this procedure survive longer than patients who do not. In addition, the benefit of the survival must be weighed in terms of the morbidity and mortality—including residual impairment—caused by the operation and by the tests done to evaluate the coronary artery anatomy in anticipation of the procedure. These would be difficult decisions even with abundant information on survival.

Should Elderly Patients With Myocardial Infarction Have Aggressive Therapy for the Prevention of Further Events?

Any intervention must balance the possible gain with the potential problems, morbidity, and mortality. Should these patients have vigorous blood pressure and cholesterol control? Should they stop smoking? Should they take β-blockers? There are some data to consider.

Does the control of blood pressure benefit the elderly? No one questions the benefit of treating severe hypertension; the benefit of treating mild hypertension is the real issue. Many studies have addressed the benefit of treating mild hypertension, but all except one, the European Working Party on High Blood Pressure in the Elderly trial,[21] focused on young and middle-aged adults.

The European Working Party on High Blood Pressure in the Elderly trial, a randomized, double-blind, placebo-controlled trial of 840 subjects who were aged 60 or older (mean age 72 ± 8 years), studied the effect of treating mild hypertension in the elderly. The trial used a diuretic combination (hydrochlorothiazide plus triamterene), with methyldopa added if the pressure was not controlled. Overall mortality was decreased 26% by treatment ($P = .077$). The numbers of cardiac deaths and of strokes were significantly reduced. A subgroup analysis of patients older than 80 years, however, did not show a benefit of the treatment.

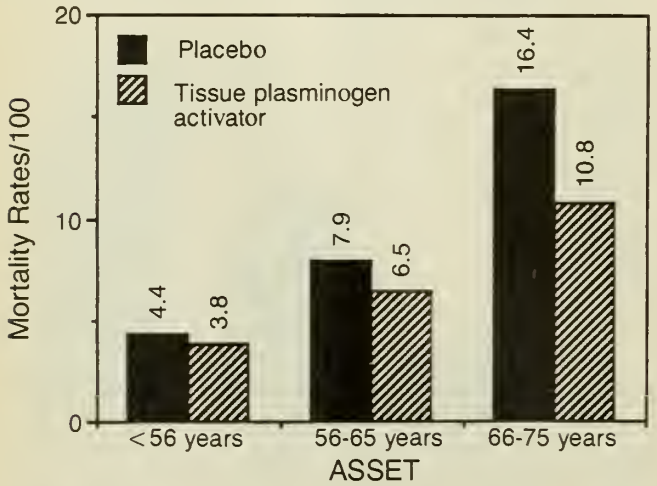

Figure 6.—The use of tissue plasminogen activator reduced mortality rates in all age groups, but the difference reached significance only in the two older groups (adapted from the Anglo-Scandinavian Study of Early Thrombolysis [ASSET][9]).

Patients who have suffered a myocardial infarction have reasons to reduce the work of the heart. Blood pressure control decreases afterload and reduces the myocardial oxygen requirement, so it appears a logical step in these patients. The survival benefit of the intervention in a large group of elderly, however, is not certain. In an asymptomatic elderly patient, the control of mild hypertension may be preferable but should not be considered imperative.

Does controlling cholesterol levels benefit the elderly? The country is currently mobilized to control cholesterol, with best-selling books proclaiming various methods of reducing cholesterol levels and manufacturers marketing oat bran in every conceivable form. All this interest has come as a result of the National Cholesterol Education Program, initiated by the National Heart, Lung, and Blood Institute in 1985. In January 1988, an expert panel appointed by the National Cholesterol Education Program promulgated guidelines for the detection, evaluation, and treatment of hypercholesterolemia.[22] The applicability of these guidelines to the elderly, however, is not clear.

The elderly have a higher prevalence of cardiac disease than younger groups. Any reduction in mortality will have a greater effect on lives saved than a similar reduction in a group with a lower prevalence of disease. On the other hand, studies suggest that a high cholesterol level is less strongly predictive of cardiac mortality in the older age groups. This diminution of effect was seen best in the data from the Framingham study[23] and the data from the Multiple Risk Factor Intervention Trial (although the upper age range for the latter trial was 57 years).[24]

There are no study findings in the elderly to support a survival advantage in subjects whose cholesterol level was lowered. Even the large trials of cholesterol-lowering agents, despite showing a 2% decrease in coronary artery disease incidence and mortality for each 1% reduction in cholesterol levels, were unable to show significant differences in mortality over the life of the trial. At this time there are no firm guidelines for the treatment of hypercholesterolemia in the elderly.

Do elderly smokers benefit from quitting? There is no doubt that smoking at any age increases a person's risk of dying of cardiovascular disease. In addition, good evidence suggests that quitting smoking confers a benefit at any age.

Jajich and associates looked at the participants of the Chicago Stroke Study, a longitudinal study of more than 2,500 people aged 65 to 74, to determine the effect of smoking on mortality in the elderly.[25] They found that smokers had a 52% higher rate of death from all causes than nonsmokers. They determined that the excess risk of death declined within one to five years after quitting cigarettes.

Investigators from the Coronary Artery Surgery Study, the large study of the effect of coronary artery bypass graft surgery on survival in patients with coronary artery disease, analyzed the effect of smoking and cessation in a cohort of almost 1,900 men and women, 55 years and older, who had angiographically proven coronary artery disease.[26] The six-year mortality rate was significantly greater in the group that continued to smoke than in the group that quit. The benefits

were significant both in the 55- to 64-years group and in the group aged 65 and older.

Should β-blockers be prescribed for elderly patients with a myocardial infarction? The use of β-blockers reduces the total mortality rate and rates of reinfarction and sudden death after myocardial infarction. Authorities currently recommend that patients without a contraindication to β-blockade should begin therapy with a β-blocker within one to four weeks after a myocardial infarction.

Do these recommendations apply to the elderly? One of the early studies, the alprenolol hydrochloride trial by Andersen and colleagues,[27] suggested that patients older than 65 years receiving β-blocker therapy had a higher mortality than the group receiving a placebo. Other trials, however, have not confirmed this finding. The metoprolol trial in patients older than 64 years showed a reduction in mortality from 14.8% to 8.1% ($P<.05$).[28] The β-Blocker Heart Attack Trial of the administration of propranolol hydrochloride in patients aged 60 to 69 years showed a significant reduction in mortality from 14.7% to 9.8% (Figure 7).[29] A Norwegian study of the use of timolol maleate in patients aged 65 to 75 years showed a significant reduction in mortality from 15.3% to 8.0% (Figure 8).[30] Elderly patients without a contraindication to β-blockers should receive β-blocker therapy after myocardial infarction.

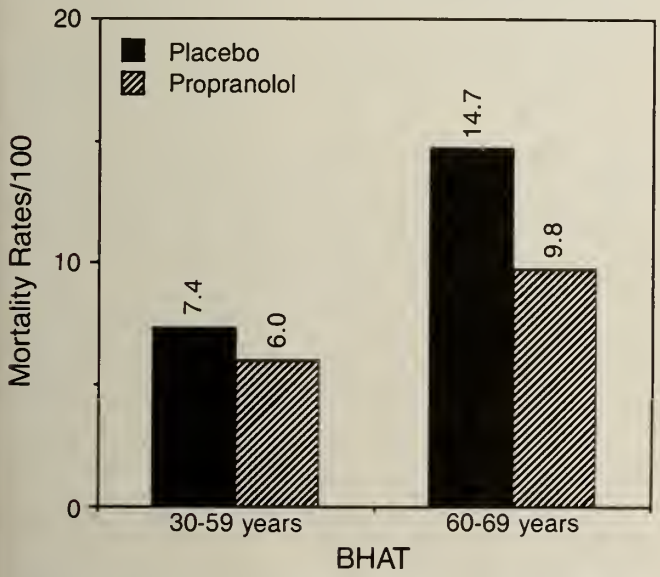

Figure 7.—Administering propranolol hydrochloride significantly reduced mortality after myocardial infarction in both age groups (adapted from the β-Blocker Heart Attack Trial [BHAT][29]).

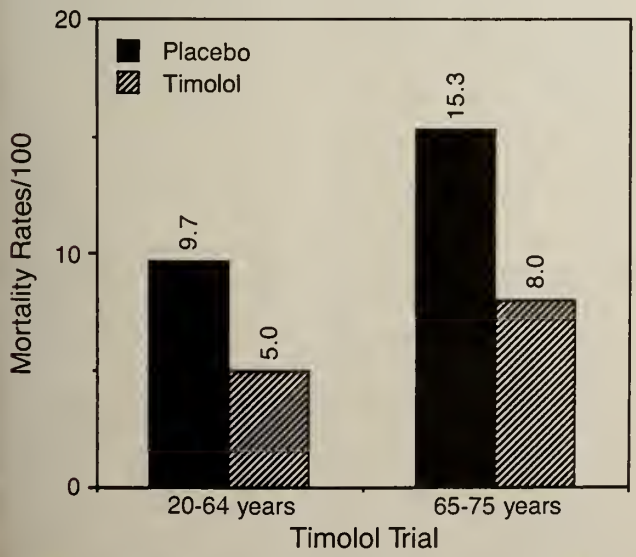

Figure 8.—Timolol maleate therapy significantly reduced mortality in both age groups (adapted from the Norwegian study[30]).

When Should Physicians Intervene?

The data on the efficacy of interventions for the treatment of myocardial infarction in the elderly are incomplete. The decisions would not be easy even with a comprehensive data base. Although the knowledge of the efficacy of an intervention is an important component of the decision, the efficacy alone does not determine the decision. Decisions about therapy in the elderly supersede *P* values, as *P* values do not indicate the best way to care for an individual patient. Aside from the efficacy of the treatment, patients' preference, a patient's quality of life, and society's policies all play an important role.

A competent patient's preference is a critically important part of any decision. The challenge of informed consent is never greater than in an elderly patient. The burden of the illness, the unfamiliarity with the hospital, and the fear of modern technology may conspire to prevent truly informed consent.

In addition to a patient's consent, physicians consider quality of life. Quality-of-life determinations, always precarious, are no easier in the elderly than in other groups. There is no easy way for a physician to decide whether treatment is prolonging the dying process or giving a patient a reasonable chance at meaningful recovery. Moreover, what physician can confidently decide the degree of dementia, if any, that disqualifies someone from aggressive, and perhaps heroic, intervention? In addition, the few studies of the effects of treatment in the elderly have focused primarily on mortality as an end point and not on how the treatment affects a patient's overall quality of life.

A final consideration is that public policy is playing an increasingly important role in the care of the elderly. Some treatments are currently rationed by age. For instance, no person aged 75 years or older qualifies for a heart transplant. The scarcity of suitable donor hearts has led to a policy that excludes patients on the basis of age even though many elderly patients would derive substantial benefit from the intervention.

Rationing by age may not end with transplantation. The debate about the use of high technology in the care of the elderly continues on other fronts. Daniel Callahan, Director of the Hastings Center (Briarcliff Manor, NY), recently wrote a provocative book, *Setting Limits,*[31] in which he proposes that health care should be rationed on the basis of age. He argues that an age-based standard for terminating life-extending treatments should be instituted. In his view, "medicine should be used not for the further extension of the life of the aged, but only for full achievement of a natural and fitting life span and thereafter for the relief of suffering" (p 53).

Furthermore, the government is demanding studies demonstrating the effectiveness of therapies in the elderly. As the movement to stop the technologic imperative gains momentum, physicians seem set for a confrontation. More expensive procedures and interventions are done just as plans are made to curtail their use. People seem to agree on general policy but cannot agree on individual cases.

The policy debate will surely continue, and a full discussion of it falls outside the scope of this article. The range of opinions is wide, and the effect on the practice of medicine is sure to be profound. Currently, however, the technologic imperative remains strong, and the impetus will continue to favor intervention over palliation.

Conclusion

Myocardial infarction is an important health problem in a rapidly growing, heterogeneous segment of our population. Clinical challenges include the diagnosis of the condition, the evaluation of treatment options, and the decision when to intervene. There are remarkably few studies of the fast-growing population older than 80 years. The small number of studies of the elderly suggest that they most commonly present with myocardial infarction with chest pain or shortness of breath. The use of aspirin and thrombolytic agents appears to have significant benefit. The role of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting in life extension is unclear. Cessation of cigarette smoking, the control of hypertension, and treatment with β-blockers almost certainly benefit the elderly in preventing future events. The role of aggressive treatment of hypercholesterolemia is undefined.

The greatest challenge in the care of the very old is deciding what treatments are appropriate. There are no easy answers to this question—especially in light of the paucity of clinical data about the efficacy of treatments in this age group. Physicians, knowledgeable about the limited literature, must make the best decisions they can, based on each patient's wishes and needs. The need for further studies of the elderly is obvious.

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Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Cognitive Therapy for Depression and Panic Disorder

COGNITIVE THERAPY is a time-limited, focused form of psychotherapy developed from the finding that psychological disturbances such as depression and panic disorder frequently involve habitual errors in thinking. The underlying theoretic rationale stipulates that the way persons feel and behave is determined by the way they structure their experiences. When patients interpret their problems as hopeless, they will feel sad; when they interpret a situation as dangerous, they will feel anxious and want to escape. Patients with panic disorder constantly misinterpret bodily and mental sensations as signs of imminent catastrophe. Numerous research studies have confirmed that a central feature of depression is the patients' belief that their past is full of failure, their future hopeless, and their present full of defeat and deprivation. They see themselves as undesirable or worthless.

The cognitions, or verbal or pictorial events in patients' streams of consciousness, are related to underlying beliefs, attitudes, and assumptions. Depressed, suicidal patients judge themselves harshly because of a belief that they are inadequate; they may fail to generate plans or strategies to deal with problems because of a belief that they are helpless, and they may reason on the basis of self-defeating assumptions. Patients with a panic disorder ascribe unexpected symptoms as signs they are dying, going crazy, or losing control.

Cognitive therapy has been used successfully for depression, anxiety, phobias, psychosomatic disorders, eating disorders, and chronic pain problems. A combination of verbal procedures and behavioral modification techniques is used within the framework of the cognitive model of psychopathology. The techniques are designed to help patients identify and correct the misinterpretations and dysfunctional beliefs that underlie the cognitions. Patients experience an abatement of symptoms by thinking and acting more realistically and adaptively with regard to their present psychological and situational problems.

More than 25 clinical trials have shown the efficacy of cognitive therapy for unipolar depression. Four studies indicate a lower relapse rate than with antidepressant drugs. In ten studies, patients had a prompt relief of panic attacks with no recurrence over a period of one to two years.

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Cross-Cultural Issues and Psychopharmacology in Asian-Americans

ASIAN-AMERICANS ARE DIVERSE and come from many countries. Many have to cope with learning English and adapting to a society that emphasizes European-American values.

Although Asian-Americans have been termed a "model minority" because of academic and work achievements, many refugee Asian immigrants suffer from posttraumatic stress disorder (9.6%) and a substantial number are unemployed (26.5%). There is a need for active outreach to reduce disabilities due to the posttraumatic stress disorder, and efforts toward fuller employment could have positive effects.

Being concerned about the stigma of mental illness, Asian-Americans do not seek services, as do whites and African-Americans, and because mental health services are less available in their home countries, there is no past experience of such use. The present effort of the National Institute of Mental Health to educate all Americans about depression represents a first step in the work that needs to be done to reduce the stigma. In addition, Asians need to be treated by professionals who can speak their languages and are knowledgeable about their cultures.

Active empathy is an important specific therapeutic need among Asians. Not only do they need empathy, as do all patients, but a therapist must actively respond by trying to reduce a troubling symptom, solve an interpersonal conflict, advise on how to cope with problems, and explain how therapy may help by reducing anxiety or depression.

Asians often require reduced doses of psychotropic

drugs. Chinese patients with schizophrenia need half of the haloperidol dosage that whites with schizophrenia do. A fourth of the Chinese, however, require dosages as high or higher than the whites. Hepatic pharmacokinetic factors and pharmacodynamic factors in dopamine receptor-mediated responses are involved in the different responses of Asians and whites to haloperidol therapy. Asians require less benzodiazepine therapy than do whites. The pharmacokinetics of alprazolam have been shown to be different in Asians as compared with in whites. Because of these differences in drug metabolism, clinicians need to be cautious about prescribing psychopharmacologic medication for Asian-Americans.

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Discontinuation and Withdrawal Problems of Alprazolam

ALPRAZOLAM (XANAX) is a triazolo benzodiazepine. In controlled studies it has been unique among the benzodiazepines as an effective agent for panic disorder and for anxiety. The low incidence of side effects and rapid onset of action make alprazolam a valuable therapeutic addition. Other antipanic agents, chiefly the tricyclic antidepressants and monoamine oxidase inhibitors, may take weeks to become effective and have many more side effects. Alprazolam has also been shown to be superior to placebo and equal to tricyclic antidepressants in the treatment of major depression, though it is not yet widely used by psychiatric physicians as a first-line drug for this disorder. No other benzodiazepine appears to share this property. The antidepressant dosage is from 1.5 to 5.0 mg per day. It is not generally recommended for simple hypnotic use, in view of a rapidly appearing tolerance and notable rebound insomnia.

Alprazolam is now widely used, and not all physicians are aware that this drug may produce physical dependence after treatment durations as short as a few weeks and in dosages as small as 0.75 to 1.0 mg per day. Alprazolam use may produce more difficult dependency and withdrawal than many other benzodiazepines, possibly owing to its very high receptor-site affinity. Withdrawal symptoms following the abrupt cessation of benzodiazepine therapy have been divided into "major" and "minor" subtypes. The major withdrawal symptoms include delirium, psychosis, and seizures. The minor withdrawal symptoms may include agitation, tremulousness, insomnia, paresthesias, confusion, generally heightened sensory perception, blurred vision, muscle cramps, muscle twitches, tachycardia, palpitations, anorexia, and dizziness. Apparent withdrawal symptoms may occasionally last considerably longer than the several weeks classically described, though these need to be distinguished (when possible) from the underlying disorder.

The textbooks have often advised tapering the dosage or detoxifying patients known to be dependent on benzodiazepines over a two-week period. This will generally not work well with alprazolam, especially when larger doses have been used. In one study of patients with panic disorder or agoraphobia treated with a mean alprazolam dosage of 5.7 mg per day for eight weeks, tapering was attempted over a four-week period. On that schedule, 35% had withdrawal symptoms. The authors recommend that tapering be extended to an eight-week period. In another report, only 4 of 18 patients with panic disorder treated with alprazolam for 12 weeks or more were able to complete withdrawal on the manufacturer's recommended reduction protocol. The package insert has been revised to recommend tapering no faster than 0.5 mg every three days. In my experience, reductions at the rate of 0.125 mg to 0.25 mg every four days are reasonable.

Patients known to be physically dependent on various benzodiazepines are often switched to diazepam therapy for detoxification, in view of the longer elimination half-life and smoother clinical course. On an equivalent weight basis, 1 mg of alprazolam has the anxiolytic activity of 10 mg of diazepam. A higher ratio than this has been reported necessary in some instances to control alprazolam abstinence symptoms, resulting in initial dose requirements for detoxification of 200 to 300 mg per day of diazepam in some patients.

There are reports of incomplete cross-tolerance between alprazolam and other benzodiazepines including diazepam. In such instances, detoxification can only be carried out with alprazolam itself.

While alprazolam is a useful drug with a unique profile, appropriate advance consideration must be given to a careful detoxification process if the drug is to be used daily in dosages of 0.75 mg per day or more and for more than several weeks.

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Geriatric Psychopharmacology

PSYCHOPHARMACOLOGIC INTERVENTIONS are common in elderly patients despite their increased sensitivity to side effects. Nearly a third of older patients admitted to hospital for medical or surgical care receive psychotropic drugs; the frequency for the institutionalized elderly is more than 90%.

Because physical illness is likely in the upper age groups, comprehensive evaluation and treatment of underlying medical conditions that may cause mental symptoms are essential before initiating any medication treatment. These physical illnesses and physiologic changes associated with aging will alter drug absorption, distribution, metabolism, and excretion so that the response to drug therapy and toxicity varies. Dosages, therefore, should begin at a lower range than for

younger adults and be increased gradually to minimize side effects and identify low-dose responses.

Although few data are available from well-controlled clinical trials, these findings and clinical experience indicate that most psychotropic drugs used for younger adults are also effective in elderly patients. The choice of a particular medication depends on its side effects, given the similar efficacy within psychotropic drug classes. A low dosage of a high-potency neuroleptic drug, such as 0.5 mg to 2 mg of haloperidol in 24 hours, may lessen agitation and psychosis and have minor anticholinergic and cardiovascular effects. A clinician should reassess efficacy over time, however, because akathisia or motor restlessness develops in many patients, which is sometimes confused with the underlying agitation. Clinical trials indicate that antidepressant response rates for geriatric depression range from 30% to 80%. Tertiary amine tricyclic antidepressants, such as doxepin hydrochloride starting at a dose of 25 mg, appear to help agitated depressions; secondary amine agents, such as nortryptiline hydrochloride, tend to decrease retarded depressions. Benzodiazepines are useful in treating insomnia (for instance, temazepam, 15 mg an hour before bedtime) or daytime anxiety (lorazepam in 0.5-mg increments). Benzodiazepines with long half-lives tend to accumulate in the blood, are more likely to cause side effects, and their use should be avoided.

Nonpharmacologic measures should always be attempted before using medications and often complement pharmacologic approaches. Psychotherapy is effective for many forms of geriatric depression. Anecdotal reports suggest that insomnia sometimes abates with such simple remedies as eliminating daytime napping and taking hot milk and tryptophan, 0.5 to 1 gram, at bedtime, although definitive data from controlled studies are lacking.

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The Homeless Mentally Ill

HOMELESSNESS among mentally ill persons is but one symptom of the lack in this country of a comprehensive system of care for the chronically mentally ill generally. With the advantage of hindsight, we can see that the era of deinstitutionalization was ushered in with much naivete and many simplistic notions about what would become of the chronically and severely mentally ill. The importance of psychoactive medication and a stable source of financial support was perceived, but the importance of developing such fundamental resources as supportive living arrangements was often not clearly seen or at least not implemented. "Community treatment" was much discussed, but there was no clear idea what it should consist of. The resistance of community mental health centers to providing services to the chronically mentally ill was not anticipated, nor was it foreseen how reluctant many states would be to allocate funds for community-based services.

In the midst of valid concerns about the shortcomings and antitherapeutic aspects of state hospitals, it was not appreciated that the state hospitals fulfilled some crucial functions for the chronically and severely mentally ill. The term *asylum* is in many ways an appropriate one, for these imperfect institutions did provide asylum and sanctuary from the pressures of the world with which, in varying degrees, most of these patients are unable to cope. Further, these institutions provided such services as medical care, patient monitoring, respite for patients' families, and a social network for the patients, as well as food, shelter, and needed support and structure.

In the state hospitals, the treatment and services that did exist were in one place and under one administration. In the community, the situation is very different. Services and treatment are under various administrative jurisdictions and in various locations. Even mentally healthy persons have difficulty dealing with a myriad of bureaucracies, both governmental and private, and getting their needs met. Further, patients can get lost easily in the community compared with a hospital—they may have been neglected, but at least their whereabouts were known. It is these problems that have led to the recognition of the importance of case management. Many of the homeless mentally ill would probably not be on the streets if they were part of the caseload of a professional or paraprofessional case manager trained to deal with the problems of the chronically mentally ill, to monitor them—with considerable persistence when necessary—and to facilitate their receiving services.

The concept of asylum and sanctuary becomes important because while some chronically mentally ill patients eventually attain high levels of social and vocational functioning, many others cannot meet simple demands of living on their own, even with long-term rehabilitative help. Many consciously limit their exposure to external stimuli and pressure, not from laziness but from a well-founded fear of failure. Professionals must realize that whatever degree of rehabilitation is possible for each patient cannot take place unless support and protection—whether from family, treatment program, therapist, or board and care home—are provided at the same time. If we do not take into account this need for asylum and sanctuary in the community, living in the community at all may not be possible for many patients.

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Neuropsychiatric Aspects of HIV Infection

PROFOUND PSYCHIATRIC and neuropsychiatric complications of the acquired immunodeficiency syndrome (AIDS) have been recognized since this condition was defined in 1981. Organic mental syndromes include affective, delusional, and dementing disorders. A primary AIDS dementia complex, related to direct effects of human immunodeficiency virus type 1 (HIV-1) on the central nervous system, has been described. It may affect about a third of all patients with AIDS and involves deficits in remembering, concentrating, and learning new information, mental slowing, and mood and motor symptoms all in the presence of a clear consciousness.

Currently in question are how early, and under what circumstances, infection with HIV-1 involves the central nervous system and how this relates to psychiatric morbidity. Early entry into the central nervous system appears to be

common, and several laboratories report detecting HIV-1 in the cerebrospinal fluid of as many as 50% of asymptomatic seropositive persons. At present there appears to be no association between neurological, neuropsychological, and brain imaging abnormalities and the recovery of virus from the cerebrospinal fluid.

Although there is general agreement that cognitive impairment is prevalent in patients with AIDS, controversy exists about such deficits in earlier stages of HIV disease. Differences in the design of investigative protocols and the interpretation of data have clouded this issue. Some evidence suggests that the rates of cognitive impairment may well increase with advancing clinical stages and that impairment may appear before clinical evidence of severe immunosuppression.

The few systematic studies of the prevalence of psychopathology in HIV-1-seropositive persons indicate rates of 25% for anxiety disorders and 15% for major depression. These exceed the point prevalence in the general population but are in the range reported for persons with other serious medical illnesses. Generally, rates of psychopathology are as high in patients with early infection as in those with advanced stages of illness. Rates of suicide may increase with HIV-1-seropositivity or AIDS. The symptomatic treatment of these psychiatric syndromes uses conventional psychotherapeutic and psychopharmacologic approaches and can be highly effective.

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Residual Attention Deficit Disorder

IN THE REVISED THIRD EDITION of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM III-R), the DSM III term of attention deficit disorder, residual type, was renamed attention deficit hyperactivity disorder, residual state. Both the DSM III and DSM III-R recognized the existence of the disorder in adults, but it is still listed among disorders first manifested in childhood. It is now recognized that the disorder commonly occurs in the adult years.

Most adults with the disorder complain of attentional and concentration difficulties, restlessness and being fidgety, impatience and a low frustration threshold, and stress intolerance. Often they have associated symptoms of anxieties, depression, mood swings, and alcohol and drug dependence. Often the presenting complaints are temper outbursts and difficult marital or work relationships. The most common co-diagnosis is generalized anxiety disorder. The general anxieties these patients have are of the milder ones and are not usually associated with phobic, panic, and obsessive-compulsive disorders. When phobias, panic disorders, and the like are present, they are often of a mild type. The alcohol and drug dependence is not of the hard-core type, but drugs are sometimes self-administered to help them function. Because of the varied presenting problems and the associated morbidity, it is essential to do a comprehensive diagnostic evaluation that may include a structured interview, rating scales, information from parents, if available, and occasionally a continuous performance test of attention and impulsivity, modified for adults. A comprehensive diagnostic workup is of paramount importance because the treatment of the disorder varies with the associated symptoms. The majority (50% to 60%) of patients with the attention deficit hyperactivity disorder, residual type, respond to the use of psychostimulants—dextroamphetamine, methylphenidate hydrochloride, and magnesium pemoline—in dosages similar to those used in children. A substantial number, especially those with depressive and anxiety symptoms, respond to antidepressant medication such as tricyclic antidepressants (desipramine hydrochloride) and the monoamine oxidase inhibitors (tranylcypromine sulfate). When alcohol or drug abuse is present, treatment is initiated with either pemoline or with desipramine. After six months to a year, if the patient stays off unprescribed drugs while the symptoms of the attention deficit disorder persist, a trial of psychostimulants may be given.

Treatment with medication should be considered as only one approach among many. Individual, family, and group therapy and other methods suited for the associated conditions should be a part of a comprehensive treatment program.

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Seasonal Affective Disorder and Light Therapy

SEASONAL AFFECTIVE DISORDER, characterized by depression during the winter months, has been actively investigated for the past six years. Virtually every study examining this disorder has found that, compared with treatment with dim light, bright light (>2,500 lux) causes clinical improvement. Therefore, the bulk of the more recent research has focused on two questions, one research oriented, the other clinical: What is the mechanism of light's efficacy? and What is the best way to administer light—what time of day and how many hours per day?

Currently no theory consistently explains all the clinical data on light's efficacy. The most prominent explanation focuses on the effect of bright light on the circadian rhythm of the secretion of melatonin, a hormone produced by the pineal gland. Mediated by pathways beginning at the retina and continuing to the suprachiasmatic nucleus of the hypothalamus and terminating at the pineal gland, melatonin production is suppressed by bright light. Melatonin has a characteristic diurnal pattern even in the absence of bright light, with measurable levels at night diminishing to undetectable levels during the morning. Patients with seasonal affective disorder show evidence of phase-delay—that is, events occur later than usual, such as being hypersomnic, which can be viewed as being phase-delayed in the time of awakening—in the secretion of nocturnal melatonin. Bright light given in the morning causes a phase-advance in this secretion, thereby normalizing the circadian rhythm of melatonin. According

to the theory, this phase-advancing of the melatonin cycle is what causes clinical remission in these patients.

Others, however, point out that many of these patients show improvement if given light in the middle of the day or in the evening—times at which melatonin secretion is virtually nil and when light would not cause a phase-advance in melatonin circadian rhythms. The mechanism by which bright light causes clinical effects must therefore be due to another nonmelatonin pathway. At present, no satisfactory explanations for this midday effect exist.

Questions on how best to administer light partly hinge on the explanation used. Proponents of the phase-shift theory recommend that light be given in the early morning, but others think that the timing of the light—morning versus evening versus afternoon—is probably irrelevant. At least 2,000 and preferably 2,500 lux of light is necessary. With the "light boxes" commercially available, patients need to sit 1 m (3 ft) from the light source. No room lights are ever bright enough to cause clinical improvement. Most investigators recommend that at least two hours of light be administered daily. A clinical response is typically seen within days to one week, faster than responses seen with the use of antidepressants. If the light therapy is discontinued while patients are still vulnerable to depression (typically before March or April), they frequently relapse quickly, usually within days.

Current research is focusing on psychopharmacologic treatments of seasonal affective disorder, the use of light for nonseasonal depressions, and further clarification of light's therapeutic mechanism of action.

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Intractable Depression in Tertiary Care

ALMOST ALL STUDIES of antidepressant use show a consistent response rate of 60% to 70%. Such results are achievable with the first or second trial of standard heterocyclic antidepressants, if therapeutic doses are achievable and the medication trial lasts four to six weeks. An apparent nonresponse should first be addressed by reevaluating for depressogenic factors, especially concurrent medication use—clonidine hydrochloride, β-blockers, methyldopa, reserpine, and birth control pills—and occult hypothyroidism. Blood concentrations provide useful information for only a few antidepressants—nortriptyline hydrochloride, imipramine hydrochloride, desipramine hydrochloride—because of the paucity of well-controlled studies. Once the above considerations have been met, patients can be defined as treatment resistant, and a systematic approach for subsequent interventions is then required. The following treatment regimen should be considered: adding lithium carbonate, adding a stimulant, the use of a monoamine oxidase inhibitor, the use of alprazolam, and electroconvulsive therapy. There are no modern studies that directly compare the relative efficacy of these interventions for intractable depressions—other than electroconvulsive treatment and monoamine oxidase inhibitors—so the choice of order is left to clinical judgment. Lithium is added to the heterocyclic antidepressant therapy at dosages needed to achieve therapeutic serum concentrations—about 0.5 to 1.0 mEq per liter—or at some centers a standard 900 mg per day is used. From 30% to 50% of patients may be expected to respond over a period of four to six weeks of combined treatments, are maintained on both for the usual 9 to 12 months, and then the dosages are tapered.

A monoamine oxidase inhibitor may be either added to, or used instead of, a heterocyclic antidepressant. Two such drugs, phenelzine sulfate or isocarboxazid, are now commonly added to a heterocyclic antidepressant regimen, but combinations with tranylcypromine sulfate have been associated occasionally with adverse effects. More than 70% of patients who apparently do not respond to heterocyclic antidepressant medication have been responsive if adequate dosages of monoamine oxidase inhibitors are used, such dosages commonly exceeding 75 mg a day of phenelzine or 50 mg a day of isocarboxazid or tranylcypromine.

Although there are few double-blind trials, many recent case series document the efficacy and safety of stimulants as antidepressant agents. This is particularly so for patients with medical illnesses, where response rates may approach 70%. Side effects are remarkably rare, as is any tendency for patients to abuse the agents. The common dosage range of methylphenidate is 5 to 20 mg twice a day and of amphetamine, 2.5 to 15 mg twice a day. They commonly are added to a regimen of heterocyclic antidepressants and may decrease the incidence of the development of tolerance.

Several large well-controlled studies have found alprazolam to be effective for depression at mean dosages of 3.0 mg per day, with a wide variance. Improvement occurred over three to six weeks. While alprazolam does not have the common heterocyclic side effects on the cardiovascular system and parasympathetic systems, its dosage should be tapered slowly to avoid possible withdrawal symptoms.

Electroconvulsive therapy appears to be the modern treatment of choice for severe or intractable depression, with typical response rates of 90% using modern computerized equipment. Accepted practice now would include it as an early intervention before all possible pharmacotherapeutic combinations are tried.

The adjunctive use for an antidepressant response of tryptophan, phenylalanine, thyroid hormone, estrogen, reserpine, yohimbine, and carbamazepine is not yet well documented.

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Reporting Elder Abuse

ALTHOUGH ESTIMATES on the prevalence of elder abuse vary, it is thought to be at least as common as child abuse. Victims are typically older than 75 years, women, and either physically or mentally disabled. Victims of abuse often come to

the attention of health providers who may have an obligation to report the problem.

Over the past ten years most states have adopted mandatory reporting laws for elder abuse. Definitions of abuse and reporting requirements may vary from state to state, but many are patterned after those developed in California. Although elder abuse is broadly defined in California to include physical abuse, neglect, mental abuse, and exploitation, only physical abuse that includes battery, sexual assault, and unreasonable physical restraint has a mandatory reporting requirement. Other forms of abuse may be reported, but there is no legal requirement to do so.

Instances of elder abuse may be reported to the police or to the county adult protective services office nearest the victim's residence. Some counties in California have "elder abuse hotlines" to provide information or take reports. All telephoned reports must be followed up by a written report using an elder-abuse reporting form, which should be available in hospital social work offices or from adult protective services offices. Anyone who reports elder abuse is immune from any criminal or civil actions, and failure to report physical abuse can result in a fine, imprisonment, or both.

Caring for victims of elder abuse is generally a team effort. A careful medical evaluation and the identification of factors that led to the abusive situation by a trained social worker are important. Reporting elder abuse is an important first step in providing relief for the victim, mobilizing community resources, and documenting what promises to be a growing problem.

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Treatment of Chronic Pain With Psychotropic Drugs

THE USE OF psychotropic drugs in the management of chronic pain is widespread. The associated symptoms of depression, anxiety, and agitation that often accompany the principal physical symptom of pain have naturally led to the use of antidepressant and tranquilizing agents. In a recent survey, tricyclic antidepressants were used by nonpsychiatric physicians 30% of the time for pain compared with 56% for treating depressions.

Many other psychotropic drugs, such as the neuroleptics, chlorpromazine and lithium carbonate, have been used enthusiastically but with varying results. Monoamine oxidase inhibitors are effective, but their use is limited by substantial food and drug interactions. Only the tricyclic antidepressants have routinely proved effective. In numerous clinical trials these medicines produce a measurable improvement in patient functioning and pain reduction of about 66% compared with 33% for placebo. Even cortical evoked potentials in experimentally produced pain in human subjects responded as well to the use of imipramine hydrochloride as to meperidine hydrochloride.

The possible mechanism of action to account for the success of the antidepressants has been reviewed. Many think that chronic pain is simply a depression-equivalent disorder and therefore responsive to the use of antidepressants. Studies with animal models, however, have shown the potent analgesic properties of these drugs.

For treatment, the more serotonergic antidepressants such as amitriptyline hydrochloride, imipramine hydrochloride, and doxepin hydrochloride are preferred by most clinicians. The fact that these drugs are sedating can be used to great advantage when they are given at bedtime. Some patients will prefer the adrenergic antidepressants such as desipramine hydrochloride and nortriptyline hydrochloride. The usual dose varies from 25 mg to 100 mg at bedtime. Trazodone hydrochloride, a nontricyclic antidepressant with minimal anticholinergic side effects, has been used with excellent results in more than 200 patients.

Primary care providers must not expect any psychotropic medicine by itself to treat chronic pain. Success requires a comprehensive management of the whole patient and a thoughtful tactical plan emphasizing patients' active participation.

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Social Rehabilitation of Schizophrenia

PSYCHOSOCIAL REHABILITATION has been shown to augment antipsychotic medication regimens in improving the course and outcome of schizophrenia. Antipsychotic medication can diminish symptoms—especially the specific symptoms of the disorder—and rehabilitation efforts can reduce or compensate for social and occupational disability and handicaps. Rehabilitation strategies assume two forms: educational and skill-building methods to increase patients' behavioral repertoires, and supportive methods to buffer the stressful effects of environmental demands and to provide social aids for overcoming disabilities.

Social skills training has been used in both hospital and community settings to facilitate patients' acquiring and maintaining interpersonal behaviors. Using instructions, modeling, behavioral rehearsal, feedback, and homework, a wide range of interpersonal and coping skills can be taught in a modular format with prescribed content areas and learning exercises. A skills training module consists of a trainer's manual, a patient's workbook, and a professionally produced videotape for demonstrating the desired skills. Because they are highly structured and prescriptive in their methods, modules can be used by an array of professionals and paraprofessionals to teach such relevant skills as medication self-management, symptom self-management, grooming and self-care, social problem solving, family coping, and conversation. Specific skills are taught; for instance, in medication management, patients learn the therapeutic and side effects of neuroleptic medication, how to monitor drug benefits and side effects, and how to negotiate medication issues with a physician. Skills training has been useful in vocational rehabilitation—that is, training participants in job-finding and job-maintenance skills.

Strategies have been developed to improve the family's

interactions with a schizophrenic patient, thereby decreasing the family burden and enhancing the patient's support network. Behavioral family management begins with factual discussion and education regarding the causes and characteristics of the disease. The effects of medication are discussed, and the family is enlisted in gaining a patient's cooperation with administering drugs. Families are subsequently trained in communication skills that can improve the emotional climate at home and to equip all family members with the problem-solving skills required to modulate stressors in the future. ("Modules for Training Social and Independent Living Skills" can be obtained from Psychiatric Rehabilitation Consultants, Camarillo-UCLA Research Center, Box A, Camarillo, CA 93011.)

Case management that bolsters strained support networks provides a fixed and continuous point of responsibility for professional care-giving and an orchestration of a broad spectrum of medical and psychiatric treatment, social services, and rehabilitation efforts. Case managers can aid the patients' course through the red tape of various agencies and coordinate the implementing of treatment by various service providers. Good case management is longitudinal, following a patient into and back out of the hospital, thereby continuing a person's links with family, professional, and community support services.

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Pharmacologic Treatment of Cocaine Dependence

THE GROWING INTEREST in the pharmacologic treatment of cocaine dependence reflects the often disappointing results obtained with current psychosocial treatment approaches such as group and individual psychotherapy, behavior modification, and Cocaine Anonymous. Various pharmacologic agents are being used to try to improve the effectiveness of psychosocial treatment, usually based on neurochemical theories of the action of cocaine. No pharmacologic agent has yet been subjected to extensive, rigorous clinical trials, so there is little sound empiric evidence to support the use of any pharmacologic agent in the treatment of cocaine dependence or to suggest the optimal duration of treatment. A prudent physician must balance the possible benefits of pharmacologic treatment against the possible risks, which include medication side effects, toxic interactions with cocaine if a patient relapses, and distracting a patient from the psychosocial aspects of treatment.

The most popular pharmacologic treatment approach is the use of cyclic antidepressants, which mimic the action of cocaine in blocking presynaptic neurotransmitter reuptake. These agents were first tried during the acute withdrawal phase because of the depression and anhedonia—inability to experience pleasure—common among newly admitted cocaine addicts. Although this depression is due to the cocaine dependence itself and therefore would resolve with abstinence alone, a longer term course of antidepressant medication is often useful in treating cocaine dependence. The therapeutic effect takes one to two weeks to develop and requires doses and blood levels similar to those for antidepressant action. Most patients can tolerate a rapid upward titration from the starting dose—25 to 50 mg per day—over four to seven days.

In a recently published double-blind, placebo-controlled study in outpatient cocaine addicts, administering desipramine hydrochloride—2.5 mg per kg of body weight daily—significantly reduced the craving for cocaine and cocaine use over a six-week treatment period. Several nonblind studies have also found the use of desipramine effective. There is no a priori reason why desipramine should be the only effective cyclic antidepressant, and there is anecdotal evidence that others, such as trazodone hydrochloride, imipramine hydrochloride, maprotiline hydrochloride, and fluoxetine hydrochloride, are also effective.

Another popular pharmacologic treatment approach is the use of dopamine-agonist agents such as bromocriptine mesylate and amantidine hydrochloride. The rationale for these is that their use alleviates the presumed hypodopaminergic or dopamine depletion state caused by long-term cocaine use. They may have a quicker onset of action than the cyclic antidepressants and so may be more useful during the acute withdrawal phase. A few small-scale, short-term, double-blind studies and several longer nonblind trials have found these two agents effective, but large-scale, placebo-controlled studies are just now being conducted. The effective dosage of amantidine appears to be in the same range used in treating natural or neuroleptic-induced parkinsonism—that is, 100 to 200 mg twice a day. Bromocriptine seems to be active at much lower dosages—1.25 to 7.5 mg a day in divided doses. Its use has also been reported effective in adults whose cocaine use represents self-medication for residual attention deficit disorder. One problem with bromocriptine therapy is poor patient compliance because of headache and nausea unless the dose is gradually titrated upwards over one to two weeks. Some interest has developed in the anticonvulsant carbamazepine, based on the hypothesized role of kindling in mediating cocaine effects. In a recently published, open-label clinical series, substantial decreases were reported in cocaine craving and use among outpatients taking carbamazepine, 200 to 800 mg daily.

Other pharmacologic treatments that have been tried, but for which there is little or no scientific evidence, include monoamine oxidase inhibitors, lithium carbonate, stimulants, neuroleptics, and amino acids. The use of lithium (at blood concentrations of 0.5 to 1.2 mEq per liter) may be helpful in cocaine addicts with primary bipolar or cyclothymic disorder, but it is of little benefit in others. Stimulants such as methylphenidate and amphetamine have a high abuse potential, and their use should be avoided in cocaine addicts. Neuroleptics, being dopamine receptor antagonists, block the psychotic manifestations of acute cocaine intoxication and theoretically would be useful; in fact, they apparently do not reduce the euphoric, reinforcing effects of cocaine. Amino acids such as tryptophan, 1 to 2 grams daily; tyrosine, 1 to 3 grams daily; and levodopa, 0.5 to 1 gram daily, are cheap, presumably safe, and widely marketed in proprietary mixtures, but their use has not yet been subjected to controlled studies.

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Editorials

Shifting Sands in Science

THERE ARE MANY SIGNS of a lessening of public faith in science. This disturbs scientists—and physicians to the extent that they too are scientists. There is a new scrutiny of scientific research, how it is carried out, how it is reviewed, and how it is reported. There are suspicions that some scientific research may not have been as objective as had been thought, that there may have been sloppy performance and even fraud that has gone undetected, and that bias and special interests may sometimes have unduly influenced the process or the outcome. But this is not all. There are increasingly aggressive elements in the public that for one reason or another seek to impede or block scientific research in universities and elsewhere through court actions. Sometimes they even resort to overt vandalism.

These are relatively recent phenomena. One has only to look back as far as World War II, when physical science and medical science came into the public view as never before. Through the Manhattan Project, physical science dramatically and abruptly ended that war with just two atom bombs. And during the war there were unprecedented advances in medicine and surgery and new approaches to the care of mental stress. The public was impressed. It seemed that modern science could do almost anything. Following the war enormous amounts of money were invested in nuclear and biomedical research, and very great progress was made. But the public expectations for a safe and healthy world were not realized.

It turned out that harm as well as good can come of scientific research, whether in physics or biomedical science. It also turned out that the basic knowledge upon which modern science is built was not as firm or infallible as the public had assumed. It was not clear whether the physical world was made of particles, waves, or strings, and in medical science and health care the advice or recommendations seemed to change almost too often to be trusted as truly scientific or authoritative. The methods and processes of scientific research were obviously not well understood. Perhaps these uncertainties, together with a growing realization that unpredictable harm as well as unpredictable good can come from many kinds of scientific research, are what has led to a growing uneasiness or discomfort on the part of many with science. In any case, and for whatever reason, it is clear that science and the methods of science are coming under increasing scrutiny.

The scrutiny is, of course, human scrutiny, usually by nonscientists, and one of the places it is clearly evident is in medicine and health care, where it begins with patients, goes on to the third parties in health care, then to the public, and finally to society itself. Many—perhaps most—patients have begun to play a more active role in medical decisions about their own care. Some want to direct their own care within the medical system. Others reject the medical system entirely and seek care and solace elsewhere. Third party payers scrutinize the health care given by health professionals and others and make judgments according to their own interpretations. The public, confused by the messages it gets from physicians and medical scientists, is often insecure. Society seems to have decided that medicine and health care are too important to be left to the professionals. Things are very different from the time, not so long ago, when people were comfortable with the idea that "the doctor knows best."

What is to be gleaned from all this? Perhaps medical science, and all of science for that matter, is not the rock many of us were taught to believe it was—a solid rock upon which human health and medical practice are built. Rather, it is more like the shifting sands, which may have different configurations with changing tides and changing winds. Shifting sands are not usually all that stable or trustworthy. Perhaps this is somehow sensed by patients and the public who, almost unconsciously, it seems, may be questioning or even rejecting the authority of physicians and a profession that claim to rely almost entirely on what they know or think they know of medical science. All of this is not to denigrate science or medical science, but rather to point out that there is a human component in both medicine and society that tends to examine and even to question scientists' authority. It is paradoxical that while science has made modern medicine the technologic wonder that it is, science may also be an important underlying cause of much of the criticism and distrust of the medical profession that we have today. Fortunately for physicians, their eggs are not all in one basket. They have more to give to help their patients than just their science. Perhaps more easily understood and appreciated by patients and the public are the caring and care physicians can give to those who seek their help. Caring and care have been known to be curative, as well.

MSMW

Controlling Penicillinase-Producing *Neisseria gonorrhoeae*— Does It Really Matter Anymore?

IN THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE, Kenneth Kizer, MD, and his colleagues at the California Department of Health Services report on a program to control a major extended outbreak of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and make certain recommendations for clinicians and local public health officials. They attribute a reduction of 59% in the reported incidence of PPNG to their efforts.

Although Kizer and co-workers undoubtedly have given the PPNG epidemic their "best shot," the article unintentionally raises some crucial policy questions about the value of categorical gonorrhea control measures, especially those with a focus no wider than a β-lactamase-producing plasmid, during a worldwide acquired immunodeficiency syndrome (AIDS) pandemic. With this in mind, I would like to take advantage of my editorial prerogative to comment on the origins and current status of gonococcal antimicrobial resistance in the United States, the implications they hold for California's PPNG control recommendations, and the need to better coordinate control programs for all sexually transmitted diseases including human immunodeficiency virus (HIV) infections.

In 1986 the Centers for Disease Control established the long-needed Gonococcal Isolate Surveillance Project to characterize the current resistance patterns in geographic regions of the country, monitor trends in these resistance

patterns, correlate patient characteristics and behaviors with infections caused by resistant strains, and use these data to develop national treatment recommendations. By September 1987, 21 public sexually transmitted disease clinics from around the United States were submitting the first 25 male urethral specimens of gonococcal organisms each month to one of four regional laboratories for fully standardized antimicrobial susceptibility testing. Of the first 7,974 specimens, a discouraging 52% met at least one of the surveillance criteria for resistance; 2.4% were PPNG, 3.3% had high-level plasmid-mediated tetracycline resistance, and 46% of the organisms without plasmid-mediated resistance had chromosomally mediated resistance to penicillin, tetracycline, or cefoxitin (S. K. Schwarcz, MD; J. M. Zenilman, MD; D. Schnell, PhD; et al: "National Surveillance of Antimicrobial Resistance in *Neisseria gonorrhoeae*," unpublished data, 1989).

How did we arrive in this fix? From 1945 to 1954, the first decade of penicillin treatment of gonorrhea, antimicrobial resistance and treatment failures were extremely rare. Even the smallest doses of penicillin, tetracycline, or chloramphenicol eradicated the helpless gonococcus. During the next 15 years, however, the gonococcus began to reveal its remarkable genetic resiliency. The proportion of organisms requiring more than 0.05 units of penicillin per milliliter for inhibition increased from 0.67% before 1955 to 65% in 1968-1969.[1]

This trend continued through 1972 and necessitated a number of upward adjustments in the recommended dose of pencillin from an introductory 100,000 units in 1945 to 4.8 million units of procaine penicillin G in 1972, delivered in an injection volume that threatened to exceed the full capacity of some human buttocks. Likewise, single oral doses of tetracycline compatible with gastric retention became ineffective.

This kind of resistance was chromosomally mediated and resulted from the random selection of mutants from a vast gonococcal population. There are a number of chromosomal loci involved in controlling varying levels of resistance to penicillin, cephalosporins, tetracycline, and other antibiotics. The common molecular mechanism is reduced permeability of the cell's outer membrane. Until recently chromosomal resistance tended to be relative and usually could be overcome by increasing the dosage.

Following a brief reprieve in the mid to late 1970s, probably owing to the United States' disengagement from military actions in Southeast Asia and the attendant interruption of the source of a large number of relatively resistant Asian strains, the gonococcus resumed its evolutionary march towards survival in an antimicrobial world.

In 1983 a higher level of chromosomally mediated resistance to penicillin and tetracycline was described in a single-strain outbreak in Durham, North Carolina.[2] The organisms required 2.0 to 4.0 μg per ml penicillin and 4 μg per ml tetracycline for inhibition, and most patients treated with either drug did not respond. Similar strains have since been reported from 23 states.[3] Although somewhat arbitrary, all gonococcal organisms that require 1 μg per ml or more of penicillin for inhibition and that do not produce β-lactamase have been specifically designated chromosomally mediated resistant *Neisseria gonorrhoeae* (CMRNG).

In March 1976, penicillinase-producing *N gonorrhoeae* was first recognized in the United States. The mechanism of resistance was dramatically different and resulted from the acquisition of a new plasmid that carried genes for production of a β-lactamase capable of breaking the essential penicillin β-lactam ring. This circular piece of extrachromosomal DNA may have arisen in a *Hemophilus* species and is an example of successful exchange of genetic material between unrelated species.

The incidence of PPNG rose slowly through 1979, and most cases either were from Southeast Asia or could be traced to imported cases. From 1979 through 1987, however, the annual incidence increased rapidly from less than 1,000 to more than 25,000. Penicillinase-producing *N gonorrhoeae* had become endemic in many parts of the United States and was no longer restricted to prostitute-associated outbreaks in New York City, California, and Florida. In 1986 only Nevada reported no cases, and previously spared cities such as Denver experienced extended outbreaks that continue to the present. The Denver outbreak also showed a shift to a more complex endemic pattern involving two different plasmids in at least eight genetically different strains, infecting persons from all major ethnic groups in wide areas of the city.[4]

Gonococcal organisms with plasmid-mediated, high-level resistance to tetracycline—defined as requiring 16 μg per ml or more for inhibition—were first identified in 1985 in Philadelphia and Atlanta but now have been confirmed from 17 states.[5] These organisms are designated by the acronym TRNG, even though this does not indicate the plasmid nature of resistance. Although tetracycline monotherapy will almost always fail to cure TRNG, there have been few clinically important outbreaks, presumably because most cases have been treated with the Centers for Disease Control's recommended dual therapy. Unlike chromosomally mediated resistant *N gonorrhoeae*, TRNG strains are worrisome because they arose from the insertion of a streptococcal tetracycline resistance determinant into the indigenous 24.5-megadalton conjugative gonococcal plasmid, forming a new 25.2-MDa plasmid that can facilitate its own transfer to other organisms.[6,7]

Given the genetic resiliency of the gonococcus and surveillance data documenting that more than 50% of recently identified organisms express one or more types of antimicrobial resistance, how should we control resistant *N gonorrhoeae*? In September 1987, the Centers for Disease Control published "Policy Guidelines for Detection, Management, and Control of Antibiotic-Resistant Strains of *Neisseria gonorrhoeae*,"[8] which were based on the best judgment of outside experts and staff in December 1986. Unfortunately, several of the key "guidelines" quickly proved to be either unworkable or based on faulty assumptions. In particular, they assumed that communities would have precise surveillance data to properly categorize PPNG prevalence into nonendemic (<1%), endemic (1% to 3%), and hyperendemic (>3%) areas, and that the recommended multitude of different stepped control elements were somehow appropriate to the control task. Even for the few large metropolitan areas with adequate morbidity data to determine monthly PPNG prevalence within reasonable confidence intervals, there were no empiric data to support the use of "less than 1%," "1% to 3%," and "more than 3%" divisions. More important, the assumption that PPNG prevalence, in turn, could be used as a surrogate for all types of antimicrobial resistance in areas where susceptibility testing is not available has not been supported by the findings of the Gonococcal Isolate Surveil-

lance Project (S. K. Schwarcz, MD; J. M. Zenilman, MD; D. Schnell, PhD; et al: unpublished data, 1989). The strong correlation between the presence of β-lactamase plasmids and chromosomally mediated resistance documented in the initial strains from Asia simply has been lost during the past decade of prolific genetic reshuffling.

Does controlling PPNG really matter anymore? Probably very little as an isolated program. In most areas these strains still account for only a small proportion of antimicrobial resistance. Furthermore, most antibiotics remain active against PPNG because the plasmid-specified β-lactamase hydrolyzes only penicillin and ampicillin, antibiotics that have become obsolete in the treatment of gonorrhea in much of the world. Therefore, PPNG may be less deserving of a "public health emergency" declaration and control program than many non-PPNG strains. The most important control element in the California program was the broad use of ceftriaxone, 125 mg or 250 mg given intramuscularly, which is effective at all sites of infection and against all types of resistance. It should be used wherever there is insufficient information to rule out the presence of resistant strains. A dead gonococcus cannot produce resistant progeny.

Was the California program responsible for a 59% reduction in PPNG incidence? Probably not, but without a well-matched contemporaneous control group (an unreasonable requirement) we will probably never know. Confounding variables include changes in sexual behavior of the host—such as fewer sexual partners, an increased use of condoms, and so forth—and rising levels of immunity to a recently introduced strain.[9] The epidemic curves for outbreaks of PPNG during 1986 to 1988 in Seattle[10] and other areas of the United States look quite like Figure 2 (Kizer and co-workers' article) of the California epidemic, even though specific control efforts differed or did not exist.

Finally, and most important, there is the policy issue of optimal relationships between control programs for the "traditional" sexually transmitted diseases like gonorrhea and the less traditional but more deadly HIV infections. The gonorrhea epidemic in the United States has rapidly contracted down around heterosexual poor urban minorities who have high rates of illicit drug use and prostitution to support these habits and therefore are at greatest risk of contracting HIV infections. Handsfield and associates reported that at one point during a 1987 PPNG epidemic in Seattle, an extraordinary 82% of patients gave histories of using crack or intravenous drugs or of having sexual contact with drug users.[10] At about the same time, the prevalence of HIV infections in heterosexual intravenous drug users in San Francisco increased to 12% (24% in blacks) from 6% in 1983-1984.[11] It is likely that similar HIV prevalence rates would have been found in Los Angeles patients with PPNG in 1987-1988. Until the common underlying risk behavior can be altered, the prospects for lasting control of either PPNG or HIV epidemics will remain dim. It is a hollow victory to cure someone of PPNG infection who later dies of AIDS.

Ideally, a gonorrhea epidemic—PPNG or non-PPNG—centered in poor Los Angeles minorities would be a biologic red light signaling a continuing high risk of HIV transmission and leading to a coordinated response that included not only treatment with ceftriaxone but HIV counseling, testing, and treatment; partner notification; and illicit drug counseling and treatment. The California Department of Health Services is certainly no different from most health jurisdictions throughout the world in failing to effectively integrate limited sexually transmitted disease and HIV prevention resources.

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The Clinical Dilemma of Psychotropic Drug Use During Pregnancy

THIS MONTH'S ISSUE includes an important and timely review by Guze and Guze of the use of psychotropic medication during pregnancy.

This clinical dilemma is a common one in that as many as 80% of pregnant women take prescribed drugs and up to 35% take a psychoactive drug.[1,2] Clinicians, however, must rely mostly on data from animal studies and suboptimal epidemiologic studies in humans for guidance. In their review Guze and Guze make several important points that are useful in decision making about psychotropic medications during pregnancy.

The authors remind us that it is more often a woman already taking psychotropic medications who becomes expectedly or unexpectedly pregnant rather than a woman already pregnant for whom psychotropic medications must be prescribed. This speaks to the critical importance of counseling a patient about safe and effective contraception if she will be taking a medication potentially toxic to her fetus.

The authors highlight the fact that risks to the fetus include not only structural teratogenic effects, direct toxic effects, and withdrawal effects but also long-term neurobehavioral effects. Such psychoteratogenicity may be expressed as disturbed psychomotor activity, faulty adaptation to the extrauterine environment, abnormal learning or problem-solving capacity, or other subtle cognitive deficits and mood disturbances. Clinicians should be aware that knowledge in this area is inadequate, and the implications for exposed

offspring are potentially grave. Not only is caution in prescribing advised, but long-term, systematic follow-up of these children is crucial.

We are reminded that most human studies on the effects of psychotropic drugs in pregnancy suffer from poor control of potentially confounding variables such as maternal age, gravidity, and parity, as well as a history of miscarriages, stillbirths, and malformed infants. Maternal nutrition, alcohol use, cigarette use, and over-the-counter and prescription drug use all need to be carefully controlled or at least matched. A mother's illness and the indication for drug use is another often neglected variable, and the length and extent of follow-up are often inadequate.

Guze and Guze wisely recommend the use of nonbiologic methods like individual psychotherapy, couples or family therapy, social casework, and hospital stays in a supportive, structured milieu before embarking on a trial of a potentially toxic medication. There are many cases in which a patient can be adequately maintained by intensive psychosocial methods and can thereby avoid the risk of drug exposure to herself and her fetus.

The authors remind us of the importance of obtaining informed consent from both the patient and her spouse, and they provide useful guidelines for explaining the relative risks and benefits of various psychotropic medications.

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Regional Chemotherapy for Hepatic Tumors?—New Hope on the Horizon

REGIONAL THERAPY for neoplastic disease by using catheters implanted either operatively or percutaneously is a burgeoning therapeutic field. In June of 1989 an international conference was held in West Germany with over 800 participants discussing just regional therapy. There is also now a monthly medical journal devoted entirely to regional therapy. Obviously it is a large subject with many different applications.

Specifically for hepatic tumors, whether primary or secondary, much work has been done in the last ten years to evaluate the regional routes of therapy, yet there are still doubts about the value of regional therapy in this setting. Enthusiasm for continuous hepatic artery infusional (CHAI) chemotherapy grew in the late 1970s because of the development of an implantable pump (Infusaid) which avoided the problems and inconvenience of an external catheter and pumping device. Before any controlled trials were begun, much less completed, thousands of these pumps had been implanted to treat metastatic hepatic disease primarily from colorectal primaries. Now ten years later we have the results of at least four randomized studies, but still the actual efficacy of CHAI on survival has not been delineated. The reason there is no clear evidence about survival is that three of the four studies had a crossover arm—that is, patients who failed systemic therapy were then given intra-arterial therapy. All four studies—at the Memorial Sloan-Kettering Cancer Center (New York), the Northern California Oncology Group (Palo Alto), the City of Hope (Duarte, California), and the Mayo Clinic (Rochester, Minn)—shared a statistically significant benefit in response rates to hepatic artery infusion over systemic therapy.[1-4] In all four studies the response to CHAI was 50% or better (response defined as at least a 50% reduction in tumor size as measured on a computed tomographic scan). The response to systemic therapy ranged from 20% to 25% or lower. From these four studies, which include over 300 patients, we can confidently say that CHAI of 2′-deoxy-5-fluorouridine (floxuridine; FUDR) will have at least a 50% chance of significantly reducing hepatic metastases from colorectal primaries. At this time there is no systemic treatment which can make this claim.

Does this response rate affect survival? The Mayo Clinic study is the only one of these four in which patients who fail the systemic arm are not treated with intrahepatic infusion. In this study there was no difference in overall survival. There was a difference in time to failure, however—14 months for hepatic infusion versus 7 months for systemic. This was a small study with only 24 patients in the hepatic infusion group; thus, it may be difficult to see a real difference in survival even if one exists.

Recently at a meeting in West Germany the preliminary results of a French randomized trial were reported. This study included 166 patients, 82 in the intrahepatic arm versus 84 in the systemic arm. This study, like the Mayo Clinic study, had no crossover in treatments. They are now seeing a significant improvement in survival in the intrahepatic arm.

The role of CHAI as an adjuvant therapy after hepatic resection was investigated by my study at the City of Hope. In one group, patients with solitary metastases from colorectal carcinoma were randomly selected to receive CHAI after hepatic resection versus resection alone. There were only 11 patients with solitary metastases, but even with this small number there was a statistically significant difference in the time to failure between these treatment groups. Patients with resection alone had a time to failure of 8.7 months versus 30.6 months for patients with resection plus CHAI. The survival, however, was not significantly different for these two groups. It was interesting to note that four of six patients with no adjuvant treatment had a liver recurrence, while only one of the patients with adjuvant treatment had recurrence in the liver.

The next group of patients who had multiple metastases were randomly assigned to resection followed by CHAI versus CHAI with no resection. Here again the recurrence rate in the liver for those with resected disease was low—one of ten patients. This study is hardly definitive proof of the necessity of adjuvant therapy after resection, but it suggests that there may be a role for this sort of adjuvant treatment approach. All of the studies have shown that even though the liver disease can be better controlled, the patients are dying of extrahepatic metastases. Regional therapy cannot do everything; it may provide improved hepatic control, but it does not affect the systemic spread. In the future, all regional treatment will have to combine regional and systemic therapies for improved patient survival.

The route of regional therapy for the liver has also been a subject of debate. Whether arterial therapy is better than portal therapy has not been studied in a randomized fashion, but there are reasons not to use portal therapy. Portal infusion has not given the high response rates of arterial therapy.

Experimental studies of hepatic tumor blood supply show that 90% of tumor vascularity comes from the hepatic artery. When different labeled substances are injected intraportally and intra-arterially, the tumor is found to contain the arterial label in much greater quantities than the portal label. Several studies on adjuvant therapy using the portal route have shown no effect. Thus, at this time intraportal therapy remains experimental and inferior to the arterial route.

Chemoembolization of hepatic tumors has recently become more popular because of the new embolic particles available. Many reports have been presented about this technique and its applications. The Japanese have published results of several studies on hepatocellular carcinoma treated with embolization and chemotherapy. In 1983 in a study of 120 patients with unresectable hepatoma, 75% of the patients had a partial response to embolization with Gelfoam and mitomycin or doxorubicin.[6] Another Japanese study had equally good results with ethiodized oil (Lipiodol) and cisplatin followed by Gelfoam.[7] At this time a randomized study comparing chemoembolization against hepatic artery infusion or systemic therapy does not exist and the efficacy of such treatment awaits delineation by such a study.

Finally, the technique of angiographic embolization for liver metastases developed from work on hepatic artery ligation as a treatment of metastases done in the 1950s. Most studies included ligation with infusion so the benefit of pure ligation was difficult to ascertain. Hepatic artery ligation has been used more frequently in neuroendocrine tumors because of their increased vascularity. In a series from the Mayo Clinic, seven of ten patients had complete relief of symptoms from the carcinoid syndrome after operative ligation of the hepatic artery.[8] The problem with ligation is that collateral growth quickly reestablishes tumor vascularity. Repeated embolizations could reduce this revascularization and get the same benefit as ligation. In a study from MD Anderson Hospital (Houston), 22 patients with metastatic islet cell tumor had multiple embolizations with 12 (54%) partial responses and a median survival of 33 months.[9] Other studies in patients with neuroendocrine tumors showed similar responses. It seems that hepatic artery embolization is an effective treatment of hepatic metastases from neuroendocrine primaries and should be considered a part of the present-day therapeutic armamentarium.

In summary, the treatment of hepatic primary and secondary tumors by means of transcatheter infusion of chemotherapy or embolic substances is an expanding and exciting new field that carries much promise for regional control. This therapy does not replace surgical resection when feasible but may be used adjunctively with surgery for increased local control. The future of these methods and their ability to produce complete and lasting responses, however, depend as always on the discovery of new agents, either immunological or chemotherapeutic, that will be more effective against malignant tumors than present-day therapies.

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Case Reports

Systemic Lupus Erythematosus Presenting as Hypoglycemia With Insulin Receptor Antibodies

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ANTIBODIES to the insulin receptor have been described in several diseases including diabetes mellitus with acanthosis nigricans,[1] Hashimoto's thyroiditis,[2] primary biliary cirrhosis,[3] progressive systemic sclerosis,[4] Sjögren's syndrome,[5] and systemic lupus erythematosus.[6-8] These antibodies have been shown to produce hyperglycemic episodes,[1,4,5,8] hypoglycemic episodes,[2,3,6,7] or both,[9,10] in a given patient. Rarely has an antibody to the insulin receptor with documented hypoglycemic episodes been described as a presenting symptom in a patient with systemic lupus erythematosus.[7]

Report of a Case

The patient, a 24-year-old woman, was referred for evaluation of hypoglycemia. She was nine months postpartum and had had episodes of extreme sleepiness, agitation, and drenching sweats that usually occurred between 7 and 9 AM. During one episode her plasma glucose level was recorded as 35 mg per dl,* and her symptoms resolved after she was given a solution of 50% dextrose in water intravenously. She said she had no other concurrent symptoms except for bilateral knee swelling, which had responded to a short course of a nonsteroidal agent. At the time of her evaluation she was no longer taking any medication and had no access to insulin or other oral hypoglycemic agents.

Her medical history included a diagnosis of discoid lupus erythematosus made three years previously based on the findings of a skin biopsy and a serologic screen. The antinuclear antibody (ANA) titer was positive at a dilution of 1:64, and only antibodies to ribonucleoprotein were identified. Therapy was instituted with topical steroids and hydroxychloroquine (Plaquenil) sulfate for a short time.

The findings of a physical examination were within normal limits except for diffuse adenopathy. Laboratory values were normal for a complete blood count, platelet count, and erythrocyte sedimentation rate. A random glucose level was 59 mg per dl. Serum chemistry levels were normal except for an aspartate aminotransferase level of 47 IU per liter (normal 6 to 30), an alanine aminotransferase value of 55 IU per liter (6 to 45), and an alkaline phosphatase level of 393 IU per liter (64 to 238). The results of a urinalysis and thyroid function tests were normal. A serum screen was negative for oral hypoglycemic drugs.

The patient was admitted for a 72-hour fast, and serial glucose, insulin, C-peptide, and cortisol levels are shown in Table 1. Computed tomography of the abdomen revealed retroperitoneal adenopathy with no definite pancreatic abnormality. A lymph node biopsy specimen showed follicular cell hyperplasia. The patient was discharged without a definite diagnosis but, because of the presence of adenopathy, was thought to have a malignant lesion. She was instructed to eat frequently, including a nighttime snack.

A subsequent bone marrow biopsy specimen revealed trilineal hyperplasia and a single benign lymphoid aggregate. A second lymph node biopsy confirmed the presence of benign follicular hyperplasia, and a second computed tomographic scan of the abdomen was unchanged. The mild liver function test abnormalities persisted, and changes on serum protein electrophoresis were consistent with inflammation. With the institution of frequent feedings, the symptomatic episodes of hypoglycemia decreased in frequency but did not resolve completely.

Four months after the initial evaluation, arthritis of the hands, pleuritis, and low-grade fever developed. A second ANA titer was done and was 4+ positive at a dilution of 1:256 with a fine speckled pattern. Both anti-Sm and anti-ribonucleoprotein antibodies were identified. A complete blood count now showed leukopenia and lymphopenia. A diagnosis of active systemic lupus erythematosus was made based on the presence of a positive ANA titer and specific anti-Sm antibody, pleuritis, arthritis, and leukopenia. Initial therapy with nonsteroidal agents was unsuccessful, and the patient was placed on a regimen of prednisone, 20 mg daily, with the complete resolution of the laboratory abnormalities, fever, and symptoms of hypoglycemia.

Five months after starting steroid therapy, the patient had an increase in activity of her lupus marked by an increase in double-stranded DNA binding and decreased C3 and C4 levels. At seven months, she experienced neurologic symptoms consisting of transient aphasia and right arm numbness and tingling. Computed tomography of the head revealed moderate volume loss without focal findings. At this point the patient moved and is no longer followed at our institution. At no point after initiating steroid therapy did symptoms of hypoglycemia recur.

Antibodies to the insulin receptor were measured using the binding-inhibition assay. Briefly, aliquots of serum and cultured lymphocytes were suspended in plastic culture tubes, set up in duplicate. The cells are incubated for two hours at room temperature, and then the supernatant is discarded. Insulin labeled with iodine 125 is then added to the cells, and unlabeled insulin is added to one of each pair of duplicate tubes to estimate the nonspecific binding of ^{125}I-labeled insulin. After incubation for three hours at 15°C, cell-associated radioactivity is measured in a gamma counter.[11]

A serum specimen obtained before therapy contained in-

*The laboratory values in this case report were reported by various laboratories (see Table 1) in conventional units. We have not converted these values to Système International (SI) units as to do so introduces inconsistency (C-peptide values are not easily converted) and possible errors, such as with "insulin:glucose ratio."

(Howard RL, Beck LK, Schneebaum A: Systemic lupus erythematosus presenting as hypoglycemia with insulin receptor antibodies. West J Med 1989 Sep; 151:324-326)

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TABLE 1.—*Laboratory Data Obtained After a 72-Hour Fast**

Date	Time	Glucose, mg/dl	Insulin, μU/ml†	C-Peptide, ng/ml‡	Cortisol, μg/dl	Insulin: Glucose Ratio	Symptoms
Day 1	1700	43	12	0.7	..	0.28	No
Day 1	2200	42	2	0.3	..	0.05	No
Day 2	0100	41	2	0.5	7	0.05	No
Day 2	0330	35	3	0.4	12	0.09	No
Day 2	0530	36	2	0.4	17	0.06	No
Day 2	0920	24	5	0.5	23	0.21	Yes
Day 3	0600	78	..	...	13	....	No

*Due to the development of symptomatic hypoglycemia, the actual duration of fasting was only 20 hours.
†Insulin was measured by radioimmunoassay (Pharmacia Diagnostics, Uppsala Sweden) with a detection limit of <2 μU per ml.
‡C-peptide was measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles) with a detection limit of 0.07 ng per ml.

sulin-receptor antibodies that inhibited 54% of insulin binding to cultured lymphocytes at a 1:10 dilution of serum. A second serum specimen taken after her symptoms resolved and while she was receiving 5 mg of prednisone daily (three months after the initial specimen) contained no detectable insulin-receptor antibodies.

Discussion

Insulin-receptor antibodies were first described in 1976 in diabetic patients with type B extreme insulin resistance and acanthosis nigricans.[1] Subsequently, insulin-receptor antibodies have been reported in other disease states including Hashimoto's thyroiditis,[2] primary biliary cirrhosis,[3] progressive systemic sclerosis,[4] Sjögren's syndrome,[5] and systemic lupus erythematosus.[6-8] The presence of hypoglycemia due to insulin-receptor antibodies was first reported by Taylor and colleagues in 1982.[2] It has now been shown that the insulin-receptor antibodies have three biologic effects in vitro: they inhibit the binding of insulin to its receptor,[12] they simulate the effects of insulin on target tissues,[13] and they desensitize target tissues to insulin.[14] The ability of insulin-receptor antibodies to simulate insulin activity has been shown in vitro by the ability of antibody to stimulate the incorporation of glucose into glycogen and lipid.[2,13] Heterogeneity in the ability of anti-insulin-receptor antibody to block insulin action or mimic insulin activity has been reported.[13]

Harrison and Heyma in 1983 reported 18 documented cases of insulin-receptor antibodies.[15] Five patients were felt to have classic features of systemic lupus erythematosus. One patient presented with "reactive" hypoglycemia, and hypoglycemia developed in three patients during the course of their disease. It is not stated if these patients had features of systemic lupus. Also in 1983 Tardella and co-workers reported a case of anti-insulin-receptor antibodies and hypoglycemia in a patient with lupus nephritis.[6] The diagnosis of systemic lupus erythematosus was made three years and four months before the patient had symptoms of hypoglycemia. Moller and associates in 1986 reported the case of a patient who presented with acute hypoglycemic coma as her primary manifestation of systemic lupus.[7] This patient responded to therapy with prednisone.

The present case represents the second report of a patient with hypoglycemia due to insulin-receptor antibodies as an initial symptom of active systemic lupus erythematosus. Although the patient was diagnosed as having discoid lupus previously, she did not meet the criteria for a diagnosis of systemic lupus at that time. During the current presentation, systemic lupus erythematosus was confirmed by the presence of a positive antinuclear antibody screen and identification of the specific antibody to the Sm nuclear antigen, as well as arthritis, pleuritis, and lymphopenia.

This patient showed suppression of insulin levels in response to the development of hypoglycemia. The initial glucose value of 43 mg per dl with an insulin level of 12 μU per ml might suggest hyperinsulinism. The low C-peptide level in this specimen and the subsequent occurrence of insulin levels of 5 μU per ml or less with simultaneous C-peptide levels of less than 1.0 ng per ml effectively eliminates the possibility of hyperinsulinism. The presence of a slightly elevated insulin level in a patient with antibody to the insulin receptor has been previously described.[2] This patient was initially felt to have an insulinoma and underwent surgical treatment before the antibody to the insulin receptor was detected. Insulinoma should not be considered in the differential diagnosis of fasting hypoglycemia when insulin levels are suppressed.

The patient's hypoglycemic symptoms resolved, and the insulin-receptor antibody titer decreased with the institution of corticosteroid therapy. Similar responses to corticosteroid therapy have been reported.[2,3,7]

The presence of antibodies to the insulin receptor should be considered in any patient with unexplained hypoglycemia and features of autoimmunity or documented autoimmune disease. An early consideration of an autoimmune origin of the hypoglycemia may prevent invasive procedures and unnecessary surgical therapy.

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Haloperidol-Induced Neuroleptic Malignant Syndrome in a 67-Year-Old Woman With Parkinsonism

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THE NEUROLEPTIC MALIGNANT SYNDROME (NMS) is generally described as a side effect of neuroleptic medications characterized by hyperthermia, autonomic nervous system dysfunction, skeletal muscle rigidity with elevated creatine kinase levels, and an altered mental state.[1] The prevalence of NMS has variously been reported to be 0.07% to 2.4%, with most figures being at about 1% of patients receiving neuroleptic medications.[2-7] Caroff in 1980 reported a mortality rate of 20%, attributed to respiratory failure due to pulmonary emboli or aspiration pneumonia, cardiovascular collapse due to autonomic instability, or acute renal failure due to myoglobinuria.[8] More recent reviews have yielded mortality rates from 4% to 22%.[9-13] Pearlman's review in 1986 suggested that the mortality had decreased to 4% in the last 50 reported cases at that time, probably due to a wider recognition.[10] All of these reports have been based on retrospective case reviews, rather than on prospective studies. Caroff's review also indicated that men are affected twice as often as women, with 80% being younger than 40 years. This has led to the conclusion that the syndrome generally occurs in young men. Several subsequent reviews have also indicated about a 2-to-1 predominance of NMS in men.[10,11] Addonizio reported an age range of 12 to 71 years, however, with a mean age of 40.[14] In this series only 51% were younger than 40. Furthermore, Addonizio also reported 18 cases of NMS in patients older than 60 years.[14] This supports the viewpoint that the syndrome is more common in elderly patients than previously thought.[15,16]

We report the case of a woman in her seventh decade diagnosed with NMS and briefly discuss the points of interest in this case in relationship to the current literature.

(Ryken TC, Merrell AN: Haloperidol-induced neuroleptic malignant syndrome in a 67-year-old woman with parkinsonism. West J Med 1989 Sep; 151:326-328)

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Report of a Case

The patient, a 67-year-old woman, was admitted for a dementia evaluation, having had for the past six years a gradual, progressive memory loss resulting in placement at a nursing facility. At the time of admission, her husband was concerned about her increasing confusion and agitation, which had required medical management with haloperidol, 1 mg at bedtime, for approximately five months. In addition, a continuous "pill-rolling" tremor had developed over the past several weeks. On the initial examination, the patient was afebrile, and her blood pressure was 120/86 mm of mercury. Neurologically, she had masked facies, a "pill-rolling" tremor in her right hand with bilateral upper extremity cogwheel rigidity, and a shuffling gait. The initial impression was that of parkinsonism, idiopathic versus drug-induced. Further history revealed that most of her symptom complex preceded the use of low-dose haloperidol and favored a diagnosis of idiopathic parkinsonism with slowly progressive dementia.

Immediately after admission, the patient became increasingly more agitated, requiring additional intramuscular doses of haloperidol. On hospital day 1 she received a total of 12 mg with an additional 13 mg over the ensuing 48 hours. On hospital day 4 she was found by nursing staff to be minimally responsive, rigid, and incontinent, with a temperature of 40.5°C (104.9°F). Her blood pressure was 80/50 mm of mercury, and her pulse rate was 154 per minute. A Foley catheter was placed, and a urinalysis and subsequent culture showed no evidence of infection. A regimen of ampicillin and gentamicin sulfate was started empirically, and she was transferred to an intensive care setting where a sepsis workup, including throat, urine, sputum, blood, and cerebrospinal fluid studies, was negative. A leukocyte count was elevated at 19.1×10^9 per liter. A creatine kinase level was elevated at 2,381 U per liter with an MB fraction of 0.04. Head computed tomography and abdominal ultrasonography were negative. An electrocardiogram and a technetium Tc 99m pyrophosphate myocardial scan showed no evidence of acute ischemic changes or damage. A regimen of dopamine hydrochloride, 3 to 5 μg per kg of body weight per minute, was started for inotropic support. On the following day, the fever rapidly subsided to 38.4°C (100.1°F) and the creatine kinase value declined to 1,691 U per liter. Over the next several days, the defervescence continued and she no longer required dopamine for blood pressure support.

On hospital day 5, the antibiotic therapy was discontinued and her condition had returned to that of her baseline examination, although she was clearly left in a weakened state, requiring assistance with ambulation. On the ninth hospital day, her urine output deteriorated, causing concern about acute renal failure. Her temperature was 37.2°C (99.0°F). A urinalysis showed 30 to 40 leukocytes and 10 to 20 erythrocytes per high-power field, and the Foley catheter was removed. A subsequent urine culture grew *Escherichia coli*, and her urine output improved with a regimen of norfloxacin, 500 mg twice a day, and intravenous hydration.

During this time, a regimen of 10 mg of carbidopa and 100 mg of levodopa (Sinemet 10-100) three times a day was started, and her tremor was found to rapidly abate. A psychiatric consultation was obtained regarding continuing medi-

cation use for future agitation. Based on the hospital course, this case was felt to represent the neuroleptic malignant syndrome, and it was suggested that lorazepam (Ativan), 1 mg taken orally three times a day as necessary, could be substituted for haloperidol in case of agitation. She was subsequently discharged to the nursing facility with both her tremor and gait improved on a regimen of carbidopa-levodopa and her agitation controlled by lorazepam therapy.

Discussion

The diagnosis of the neuroleptic malignant syndrome was based in this case on the temporal onset of pyrexia, an elevated creatine kinase level, autonomic dysfunction, and characteristic physical findings that occurred after an abrupt increase in the administration of a high-potency neuroleptic medication in the absence of an infectious cause by rigorous evaluation. Previous attempts to outline rigorous guidelines for a diagnosis of NMS by retrospective review of patients diagnosed with the syndrome have met with criticism, particularly based on expanded definitions of pyrexia, an overemphasis on creatine kinase levels, and the failure to rigorously search for infectious causes.[6] In addition, the spectrum concept of NMS proposed by Keck and others has been challenged as an overinclusive definition resulting in increased prevalence figures.[4,17] As with any disease process, a variable presentation is expected depending on interpatient variation. Because the treatment of the syndrome remains primarily symptomatic, however, and numerous controlled studies of the various treatment modalities are not available, the diagnosis of NMS must remain one of exclusion after all causes more amenable to treatment have been ruled out. The increasing awareness of NMS, coupled with expanded diagnostic criteria as reported in retrospective studies, risks prospective overdiagnosis and a failure to recognize more treatable causes, in particular central nervous system infection.[2] For example, meeting previously reported criteria for NMS should not preclude a lumbar puncture in a pyrexic patient with an altered mental state. The role of an elevated creatine kinase value in the diagnosis of NMS has been challenged as being overemphasized[6]; its role in symptomatic therapy, however, should not be disregarded, as myoglobinuric acute renal failure due to rhabdomyolysis is frequently reported.[18] Indeed, emphasis must remain on early supportive care of all organ systems regardless of the diagnosis. Respiratory, cardiovascular, and renal complications remain the primary causes of death in NMS, and it appears intuitively obvious that immediate and aggressive support of all organ systems would significantly reduce the mortality associated with this syndrome.

Although the pathogenesis of the neuroleptic malignant syndrome remains unclear, it has been proposed that a rapid blockade of postsynaptic dopamine receptors by large doses of neuroleptic drugs and a hypothalamic disease may underlie this disorder.[19,20] The high-potency neuroleptics, in particular haloperidol, have been implicated as frequent offenders, although NMS has been reported with the use of most neuroleptic medications.[4,21] A pronounced reduction in symptoms has been noted with the use of bromocriptine mesylate and amantadine hydrochloride, both dopamine agonists.[10,11,13] Several authors have reported a lessening of NMS symptoms with the administration of levodopa-carbidopa combinations in patients previously administered these drugs for parkinsonism.[22-24] It is of interest that improvement was incidentally seen in the patient reported here following the administration of a levodopa-carbidopa combination for parkinsonian symptoms, although the improvement noted may be attributed solely to the withdrawal of the neuroleptic agent. She also received intravenous dopamine for inotropic support. Ungvari reported a similar case of NMS that responded promptly to the intravenous administration of dopamine.[25] In addition, this syndrome has been reported following the withdrawal of dopaminergic agonists, lending further support to the dopamine-blockade theory.[5,26] To our knowledge, a prospective study of the incidence of the neuroleptic malignant syndrome in patients with Parkinson's disease treated with neuroleptic medications for agitation has not been published. If the dopamine-blockade explanation is accurate, however, it is plausible that further dopamine blockade in the setting of preexisting dopamine depletion could precipitate the syndrome. Levinson and Simpson point out that patients with severe extrapyramidal symptoms, with or without fever, are at risk for potentially lethal complications from neuroleptic-induced dopamine blockade. They suggest the use of bromocriptine as the most rational treatment choice based on the dopamine-blockade theory.[27]

In addition to the dopamine agonists, dantrolene sodium has been used with success in treating the severe muscular rigidity and resultant rhabdomyolysis seen in NMS, based on success in treating malignant hyperthermia.[28,29] Transient relief of symptoms has been reported with the use of benzodiazepines.[11] Electroconvulsive therapy has been used with success in patients with NMS and psychosis, although serious cardiac complications have been reported.[11]

Addonizio reviewed 18 cases of the neuroleptic malignant syndrome occurring in patients older than 60 years.[14] All but four were receiving neuroleptic medications. Haloperidol was the most frequent agent implicated, although it was unclear if this was due to potent dopamine-blocking activity or to the frequency of haloperidol use in the elderly. Four of the patients were diagnosed with parkinsonism, and in three of the cases NMS occurred following the discontinuance of carbidopa-levodopa therapy. Addonizio concluded that the early recognition and discontinuance of neuroleptic medication is particularly important in the elderly population as preexisting medical illness in this age group is common and therefore they are at risk for severe morbidity and mortality.[14]

The organic brain syndrome has been suggested as a risk factor for the development of NMS.[8] In Pearlman's recent review of 330 cases, however, the coincidence of NMS and the organic brain syndrome was not significant.[10] Alzheimer's-type dementia has also been reported in several patients diagnosed with the neuroleptic malignant syndrome.[3,15,30] These patients were also receiving neuroleptic medication, and whether Alzheimer's dementia constitutes a separate risk factor for the development of NMS is not clear. Patients with the organic brain syndrome and dementia are more likely to be treated with neuroleptic medication for agitation, and this alone may constitute their increased risk.

The role of the loading dose has previously been discussed and appears applicable in this case. Although NMS has been reported in patients receiving neuroleptics for extended periods before the occurrence of the syndrome, it appears that it develops in most cases following either a change of medication or an abrupt increase in dosage, as was the case in the patient reported here.[19] The increasing use of

intramuscular haloperidol for acute agitation needs scrutiny in light of its potent dopamine-blocking properties. Perhaps a combination of a benzodiazepine with lower initial doses of the neuroleptics would be the treatment of choice in patients with acute agitation, particularly in those with extrapyramidal symptoms or patients who have had NMS previously diagnosed.

In conclusion, this case is of interest for several reasons and serves to point out several important concepts in the diagnosis and treatment of the neuroleptic malignant syndrome. The patient was an elderly woman presenting with parkinsonian features and was treated for acute agitation with a high-potency neuroleptic. She had previously received low doses of haloperidol without complications, and a direct temporal relationship exists between the increase in dosage and the onset of her symptoms. It must be emphasized that NMS is a diagnosis of exclusion, and prompt supportive therapy must be given for cardiovascular, respiratory, and renal systems in an attempt to further reduce the mortality associated with the syndrome. Recent reports indicate that the mortality rate is decreasing, probably based on an earlier recognition and a better understanding of the pathogenetic mechanism. The use of neuroleptic medications in acute agitation must be evaluated for each patient and, particularly in the presence of extrapyramidal symptoms, consideration should be given to lower initial doses of neuroleptics, coupled with the careful use of benzodiazepines, in an attempt to prevent the onset of NMS by rapid dopaminergic blockade.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Doctors, Patients, and Fear

To THE EDITOR: I find it quite incredible that an article like "Doctors, Patients, and Fear" by A. M. Levine, MD, which appeared in the June issue,[1] could be published in a scientific journal in 1989. I do not feel that any physician would argue with the general message that fear, lack of educating the patient, and not taking time to talk to the patient substantially interfere with a patient's ability to make a reasonable decision as to choice of treatment.

I do find this physician's conclusions, "apparently, when his mind was at ease, as opposed to stressed and frightened, some chemical or immunologic event must have occurred, which apparently had a positive effect on his malignant lymphoma," to be less than conclusive.

I would think that alternative conclusions, the most obvious of which would be an error in measurement and clinical assessment of organ size, would rate somewhat higher.

I do not discount the physician's "conclusion" but feel that, in this day and age of "cancer quackery," we as physicians in the scientific community should be a little more careful in our wording and interpretation of data. The art of medicine does not need to exclude scientific methodology.

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REFERENCE

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Psychiatric Manifestations of Physical Illness

To THE EDITOR: Many medical illnesses cause dysfunction in mood, thinking, and behavior and may present as depression or mania, anxiety disorders, paranoid disorders, schizophreniform disorders, or confusional states. Many patients diagnosed as having a mental disorder in fact have a physical disorder that is causing the psychiatric manifestations. Many more physical disorders cause psychiatric symptoms than was thought to be the case in the previous decade. Psychiatrists are more likely than nonpsychiatric physicians to overlook an underlying physical disorder. Nonpsychiatric physicians more frequently treat psychiatric symptoms as coincidental to, rather than as caused by, underlying physical disorders.

Eight major categories of physical illnesses are most likely to be associated with psychiatric symptoms: (1) toxic states, especially those due to alcohol, marijuana, cocaine, and benzodiazepine toxicity or withdrawal; (2) carcinoma, especially pancreatic carcinoma; (3) pulmonary diseases, especially chronic obstructive pulmonary disease and asthma; (4) cardiovascular disease, especially coronary artery disease and congestive heart failure; (5) blood dyscrasias, particularly anemia; (6) infectious disorders, particularly the acquired immunodeficiency syndrome, hepatitis, sexually transmitted diseases, mononucleosis, and influenza; (7) cerebrovascular disorders, including seizure disorders, demyelinating neurologic disorders, and encephalopathies; and (8) endocrine diseases, especially hyperthyroidism, hypothyroidism, and diabetes.

In a review of 99 patients with a diagnosis of "hysteria" observed for seven to nine years, 4 patients committed suicide, 8 died of disorders that must have been present at the time of the original diagnosis, and 22 were suffering from a major organic illness—including cholecystitis, meningitis, or Alzheimer's disease—all undiagnosed at the time. Eleven patients had schizophrenia or major depression. Out of the original group, only 20 were accurately diagnosed and 69 were inaccurately diagnosed and presumably mismanaged.[1]

More than 2,000 patients in a psychiatric clinic were studied, and 43% were found to have significant medical illness. Half of those had been undiagnosed by the referring physician. Of this group, 18% had psychiatric symptoms that were caused by the underlying physical disorder, 51% had a physical illness that existed before the psychiatric diagnosis, and in 31% the psychiatric disorder and the medical disorder were coexistent.[2]

Thus, the underdiagnosing of underlying physical illness is the rule and not the exception in patients with mental disorders.

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REFERENCES

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More on Foot Punctures

To THE EDITOR: Most of us are now aware of the association of puncture wounds to the foot through tennis shoes and pseudomonas infections. The article by Patzakis and colleagues in the May issue[1] confirms our impression of the potential dangers with such wounds.

The authors did not explain, however, what they mean by "earlier definitive treatment" to "decrease morbidity." They also mentioned that, "hospital admission at the time of the initial medical evaluation" should be considered for certain types of wounds.

I would like a further explanation of what the definitive therapy is and why a person must be admitted to hospital.

I have begun seeing all such patients in the office and attempting to debride the puncture wounds under local anesthetic. I often find small pieces of material (presumed to be part of the tennis shoe) in the puncture wound. Although my

case number is relatively small—probably eight or ten patients—I have not had a *Pseudomonas aeruginosa* infection result from any of the puncture wounds that have been debrided in the office.

Perhaps the authors could comment on the two issues I have mentioned.

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* * *

Drs Patzakis, Wilkins, Brien, and Carter Respond

To THE EDITOR: Deep nail puncture wounds of the foot are often penetrating bone or joint injuries, or both, in the zones described. The same criteria for treating penetrating injuries to larger joints apply to these smaller bones and joints. Therefore, we emphasize the importance of determining at the time of initial evaluation whether a bone and joint penetration has occurred. One should suspect joint penetration of a metatarsophalangeal joint if there are swelling and irritability due to joint synovitis. For those patients with clinical evidence of bone and joint involvement, "early definitive treatment" has required thorough surgical exploration and debridement of the joint and bone and associated nail track, with concomitant systemic antibiotic therapy. We are recommending hospital stays only for bone and joint penetration injuries.

Although the association of infection with *Pseudomonas aeruginosa* following a penetrating nail wound through a tennis shoe is well recognized, it is important to point out that this organism has also been recovered from patients with other types of foot covering.

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'Minor' Can Be a Source of Major Debate

To THE EDITOR: Drs Peterson and Altman reported in the June 1989 issue three cases in which cervical cord injuries followed what they consider to be "minor" cervical hyperextension injuries.[1] The perspective used defined minor with reference to the vertebral injury itself. In all three reported cases, however, a serious cervical cord injury occurred.

One can immediately debate whether it is appropriate to consider this a "minor hyperextension injury." According to Webster's dictionary, minor means "comparatively unimportant" and "not serious or involving risk to life."[2] This is the generally accepted meaning of the term. To apply the term minor myopically when the overall injury is serious does have some use, as revealed by the authors, but, it may also be misleading. This becomes especially relevant in a litigious society wherein truly minor injuries are often the focus of legal claims. If minor is to be used as proposed by these authors, then it is important to acknowledge the differences between this syndrome and the truly minor whiplash syndrome so commonly seen in office practice.

These cases are not similar to the typical minor whiplash injury. In all of the cases presented the patient showed immediate objective abnormality. Clear abnormalities were seen on clinical neurologic examination in all cases. And, demographically, the patients were older—the youngest being 48. In contrast, the typical minor whiplash injury involves younger patients (generally 20 to 40 years old), subjective symptoms far outweigh objective abnormalities (often to the exclusion of the latter), and objective neurologic abnormalities are absent (though subjective dysesthesias or weakness may be reported).

Clearly, the syndrome reported by these authors is not to be compared to the average whiplash syndrome. In its chronic forms, the clinical behavior of the typical whiplash syndrome is far more easily explained by an examination of social circumstance and demographics than by a laboratory examination—a personal observation, but one shared by others.[3] I think it would be an injustice to let these cases encourage the assumption that the chronic subjective whiplash injuries involve some occult similar injury. The leap to such an association is—as is claiming to be the lost heir to a fortune—very appealing to many participants of compensated injury cases.

The authors are correct when they show that cervical cord injuries may occur with relatively little injury to the vertebral architecture, but the term minor used in this context deserves caution and a recognition of its limited perspective.

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Circumcision

To THE EDITOR: We are quite disturbed by the editorial policy that allowed Dr Franzblau's letter[1] regarding a recent epitome[2] to be published. Many of his comments were directly contrary to the expressed purpose of the Epitomes section. In addition, Dr Franzblau makes statements alluding to a proved "relationship of all sexually transmitted disease, squamous cell carcinoma of the penis, and human immunodeficiency virus (HIV) infections" to the uncircumcised state, followed by the comment that the authors should perform a computerized literature search.

That Dr Franzblau's unreferenced statements run directly contrary to the new position of the American Academy of Pediatrics,[3] a position taken after an extensive review, only adds insult to editorial injury. To allow such to be published without editorial comment or a chance for the authors' rebuttal is inexcusable for the journal and a direct affront to the peer review process undertaken by the Scientific Advisory Panel on General and Family Practice of the California Medical Association.

There is not a recent, comprehensive evaluation of circumcision in the literature, though some data were recently presented[4] that support the epitome. The possible link be-

tween circumcision and sexually transmitted disease is far from determined.[3] Even if the relationship is proved, however, future sexually transmitted diseases are unlikely to have a major effect on the circumcision controversy because of discounting. Discounting is a procedure widely accepted as necessary when dealing with future health outcomes.[5] For example, assuming a discount rate of 5% (half that proposed by the US Office of Technology Assessment[6]), a 40% increase of sexually transmitted diseases in uncircumcised men has the quality-adjusted health effect of about half a well day 25 years in the future. This is hardly an argument for routine circumcision. The possible effect of circumcision on the transmission of the acquired immunodeficiency syndrome (AIDS) virus is, of course, difficult to estimate. AIDS is unlikely to be an issue for a child born in 1989 until at least the year 2005, and we have no idea what the epidemiology of AIDS will be 16 years from now.

A journal of substance should have higher standards than to allow one person's thoughts to run unopposed against careful, scholarly, peer-reviewed work. We hope this example is a momentary editorial lapse rather than a new editorial direction.

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EDITOR'S NOTE:

We appreciate the authors' careful reading of the journal and their thoughtful response.

MSMW

Acute Severe Asthma

TO THE EDITOR: There is an obvious omission in the article by Dr Franklin in the May issue.[1] No review of asthma is complete without mention of preventing attacks. An obese, smoking, beer-drinking person sleeping on feather pillows with a cat should be told that this behavior may have something to do with his or her asthma. Until this is done, the acute severe asthma is liable to continue.

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Treating Septic Prepatellar Bursitis

TO THE EDITOR: We congratulate McAfee and Smith[1] for their excellent review of a problem that we treat commonly: olecranon and prepatellar bursitis. Our institution provides medical care for a large population of active duty sailors and marines who often work on their knees and are predisposed to developing septic prepatellar bursitis. We also agree with McAfee and Smith's statements that blunt trauma, skin abrasion, or repetitive pressure applied to the knee may precipitate septic bursitis by inoculating the prepatellar space with *Staphylococcus aureus.* We take issue, however, with their claim that surgical incision and drainage are rarely necessary and may prolong the healing time.

Report of a Case

A 22-year-old sailor was referred by his ship's medical officer with a low-grade fever and anterior left knee pain that was unresponsive to a seven-day course of oral antibiotics and rest. On physical examination, the prepatellar soft tissues were swollen, red, and exquisitely tender; joint motion was painless except with full flexion, which compressed the prepatellar bursae. Needle aspiration yielded 5 ml of purulent fluid. The patient underwent surgical irrigation and debridement of the bursa through a 2.5-cm (1-in) lateral para-

Figure 1.—The surgical incision for irrigation and drainage is shown. There are also skin abrasions **(arrow)**.

Figure 2.—The specimen shows infected clot and the posterior wall of the bursa.

patellar incision using leg block anesthesia (Figure 1). In addition to further purulent fluid in the cavity, a large clot of infected necrotic bursal tissue was seen and excised from the posterior wall of the bursa (Figure 2).

Nylon sutures were placed in the skin but left untied. The wound was loosely wicked open with sterile gauze soaked in saline solution. Cultures showed a growth of *S aureus,* and the patient was treated with a five-day course of intravenous cefazolin sodium and twice-a-day whirlpool baths and dressing changes. The wound was closed on the sixth postoperative day by tying the previously placed sutures. An additional ten-day course of oral dicloxacillin was given, and the patient was discharged on hospital day 8. He healed without complication.

Discussion

Wilson-MacDonald reported that 3 of 27 patients (11%) with septic prepatellar bursitis failed repeated needle aspiration and intravenous antibiotic treatment and required surgical drainage.[2] In addition, he reported 6 patients treated initially with surgical drainage; all 9 surgical incisions healed uneventfully. Thompson and co-workers, on the other hand, reported that 2 of 5 surgically treated cases still had draining incisions at discharge. They did not report the duration of hospital stay, length of incision, or method of wound closure, however.[3]

We have no experience with Knight and colleagues' method of percutaneous placement of a suction-irrigation system using local antibiotic solution.[4] Injecting antibiotics into the bursal space has no documented efficacy for bacterial septic bursitis, however,[1] and a complicated inflow-outflow tube system provides no advantages over a simple, thorough irrigation and debridement through a small, well-placed incision. In addition, a surgical procedure may be necessary to treat secondary osteomyelitis[5] or fungal septic bursitis.[6]

In summary, when aspiration fails or when a pointing abscess exists, incision and drainage of the bursa are indicated.

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The views expressed in this letter are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

Topics in Primary Care Medicine

New Hope for Subfertile Men

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

The treatment of male infertility has been problematic. In approximately 40% of infertile men, the impairment in sperm count, motility, and morphologic features can be defined, but the cause remains unknown. In the absence of definitive pathogenesis, logical treatment is difficult. Many drugs—androgens, gonadotropins, antiestrogens—have been used empirically with varying claims of success, but the few placebo-controlled studies have failed to show any efficacy. Fortunately the remarkable advances in reproductive biology are now being applied to male infertility. These assisted reproductive techniques attempt to overcome the problems of reduced sperm motility and number.

Assisted Reproductive Techniques

The routine semen preparation for these procedures is critical and involves separating motile sperm from dead sperm, cellular debris, and other material present in semen. Seminal fluid must be removed because it contains factors inhibiting normal fertilization as well as prostaglandins, which may cause uterine cramping during intrauterine insemination. The most common procedures include "swim-up" separation, sperm washing, and the Percoll discontinuous gradient technique. Each method has advantages and disadvantages and must be selected for each individual specimen. The direct swim-up technique allows a highly motile fraction of sperm to be collected, although the number recovered is significantly less than that recovered by sperm washing or density gradient centrifugation. The washing procedure provides the highest recovery rate, but nonviable sperm and debris are collected along with the motile sperm fraction. We prefer the simple, discontinuous, two-layer Percoll density gradient. It allows the recovery of a greater number of sperm with high motility and improved function, as tested by the sperm penetration assay. Several other in vitro methods, including sperm incubation with human follicular fluid and low-temperature incubation of sperm with Tes-Tris (Test) yolk buffer, also appear to improve the functional activity of sperm as tested by the sperm penetration assay.

Intrauterine Insemination

The improved conception rate after the intrauterine insemination of washed spermatozoa from men with poor-quality semen created a resurgence of interest in this technique. Pregnancy rates per cycle for luteinizing hormone (LH)-timed intrauterine insemination versus LH-timed natural intercourse for men with semen defects were 20% (8/39) and 0% (0/38), respectively. The theoretic advantage of intrauterine insemination is that it may increase the number of sperm arriving at the fertilization site, particularly when the male partner has a decreased sperm number or motility or a low semen volume, or the female partner has impenetrable (or absent) cervical mucus or antisperm antibodies. The success of the procedure has been difficult to document because of varying indications for treatment. Most studies are uncontrolled and use varying techniques of semen processing, ovulation timing, and number of inseminations per cycle. Intrauterine insemination is particularly successful in couples with cervical-factor infertility (60% pregnancy rate), but a review of seven studies in which male-factor infertility was the cause show the pregnancy rate to be 25% (range, 7% to 66%). In attributing success to intrauterine insemination, we should not forget that treatment-independent pregnancies may occur. In a review of several large series, the spontaneous pregnancy rate was 14% in those couples discontinuing treatment.

In addition to the better semen-processing techniques now available, newer techniques to predict ovulation have also increased the success of intrauterine insemination. The ultrasonic visualization of ovarian follicular development allows the confirmation of approaching ovulation. Simple and convenient monoclonal and polyclonal antibody assay kits for urinary LH determination have recently become available. Combining ultrasonography with LH measurements results in the better prediction and documentation of ovulation. In women with irregular cycles, hormonal manipulation with human menopausal gonadotropin or clomiphene citrate and human chorionic gonadotropin has been used. In couples with idiopathic infertility, superovulation with human menopausal gonadotropin has recently shown a remarkably improved success rate with intrauterine insemination compared with intrauterine insemination alone (40.9% versus 6.7%). The duration of therapy should not be more than five months, as most studies have shown the mean number of treatment cycles required for success to be 3.5.

(McClure RD: New hope for subfertile men. West J Med 1989 Sep; 151:333-335)

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ABBREVIATIONS USED IN TEXT

ET = embryo transfer
GIFT = gamete intrafallopian [tube] transfer
IVF = in vitro fertilization
LH = luteinizing hormone

Intrauterine insemination may be an alternative before attempting the costly and complex in vitro fertilization and embryo transfer procedures or for couples who are reluctant to resort to artificial insemination by donor or adoption. For those persons with clearly defined indications, it is a potentially useful procedure, but optimism should be guarded for men with severely abnormal semen variables.

In Vitro Fertilization and Embryo Transfer

In vitro fertilization (IVF) followed by embryo transfer (ET) was originally established to solve tubal infertility problems in women with normal partners. The success of these procedures and the small number of spermatozoa required for fertilization—50,000 to 200,000 per egg—have expanded the indications for IVF to couples with male-associated or solitary male-factor infertility. The selection criteria for IVF-ET are still being defined, but oligospermia, asthenospermia, or teratospermia are the usual indications. Of the three conventional semen variables, sperm motility appears to have the most significant effect on fertilization. Although pregnancies have been produced by sperm with severely impaired motility—less than 10%—the fertilization rate is greatly decreased when the initial motility is less than 30%. Severe or moderate sperm density abnormalities ($< 10^6$ per ml) also reduce fertilization rates considerably, although fertilization has been achieved with as few as 600,000 total motile sperm per ejaculate. Fertilization rates in vitro are also lower when the male partner has more than one semen abnormality.

Once fertilization has taken place in couples with male-factor infertility, the embryos have the same potential to result in successful pregnancies as that reported for female-factor infertility when the husband is normospermic. A Norfolk (Virginia) in vitro fertilization group showed a fertilization rate of 46% and a pregnancy rate per transfer of 37% in the male-factor group and a fertilization rate of 93% with a pregnancy rate per transfer of 21% in the female-factor group. It appears that the lower chance of fertilization with poor semen is balanced by a higher rate of pregnancy in women with a normal reproductive capacity. Despite initial concerns, there has been no increase in fetal abnormalities or the rate of spontaneous abortion in the IVF-ET program.

Gamete Intrafallopian Tube Transfer

Gamete intrafallopian tube transfer (GIFT), like in vitro fertilization, requires the attainment of many mature fertilizable oocytes with hyperstimulation protocols. Gamete intrafallopian tube transfer differs from IVF in that it requires laparoscopy to transfer the gametes (oocytes and sperm) into the fallopian tube, and fertilization occurs in the body. The higher pregnancy rates with the GIFT procedure have been attributed to the placement of gametes in the normal site of fertilization or to the synchronized tubal transport of the cleaving embryo to the uterus (or both). The disadvantages of GIFT are that successful fertilization cannot be documented, the ectopic pregnancy rate may be higher, and a patient must have at least one patent fallopian tube.

Recent modifications have improved GIFT's success. Once oocytes are retrieved by vaginal aspiration, fertilization is allowed to occur in vitro, and, after development, the embryo is transferred to the fallopian tubes by laparoscopy. This technique combines the advantages of the documentation of fertilization, the elimination of abnormal eggs, and the selection of viable fertilized oocytes for intrafallopian transfer—all of which may increase the chance of implantation.

Micromanipulation. Despite the success with IVF and GIFT, additional refinements are necessary for patients whose concentrations of functional sperm are insufficient for the dispersion of cumulus cells, penetration of the zona pellucida, and fusion with the oocyte plasma membrane. Micromanipulation, an innovative reproductive technique on which human trials are now taking place, allows the surgical manipulation of oocytes. Because the zona pellucida acts as a barrier to polyspermia, its removal is undesirable, although in theory this could permit a substantial reduction in the sperm-egg ratio. Through micromanipulation, a microneedle loaded with acidic medium can be brought into contact with the zona surface, causing a localized dissolution. In studies in mice, this "zona drilling" has resulted in a high rate of oocyte survival, fertilization in vitro, and normal development at sperm concentrations 100 times lower than those in controls and with a polyspermia rate similar to that of controls.

Spermatozoa also can be injected directly into the ooplasm, bypassing the zona pellucida and plasma membrane, or into the perivitelline space. Preclinical experimentation has shown that human oocytes can survive the mechanical insertion of spermatozoa directly into the ooplasm and that both male and female pronuclei will subsequently form. Microtechniques have also been used to split two-cell embryos into 2 one-cell embryos in animal experimentation. This may be an important advance, for the retrieval of a sufficiently high number of quality ova is usually a key factor in the effectiveness of in vitro fertilization. Preliminary attempts to correct fertilization defects have also shown the potential benefit of micromanipulation. The polyspermic fertilization of human oocytes in vitro produces genetically abnormal embryos, and removing the extra male pronucleus offers another possibility that normal diploidy can be restored.

With many of these microsurgical techniques, concern remains over the genetic normality of the individually selected sperm for microinjection. Techniques for the direct analysis of chromosomes of microinjected spermatozoa are currently being developed and may assist in determining the use of microsurgical fertilization in humans. Besides the potential ethical, moral, and legal questions these techniques raise, a great deal of further experience in animals must be gained before undertaking human trials.

Electroejaculation. Until recently infertility was an almost universal sequela of spinal cord injury in men. Although this impairment was related to pathologic changes in the testes, the major impediment to procreation was the loss of the ejaculatory capacity. This requires both the sympathetically controlled process of seminal emission and the somatically induced events of ejaculation and is retained in less than 10% of such patients. Historically, various remedies have been attempted with limited success. "Electroejaculation," used successfully for many years in animal husbandry, has now been adopted successfully both for spinal-cord-injured men and for anejaculatory men who have undergone retro-

peritoneal lymph node dissection. Through a rectal probe, an electric current stimulates the postganglionic sympathetic nerves that innervate the prostate and seminal vesicles. At the University of Michigan, a successful electroejaculation program has been underway for the past several years. In men with cervical, thoracic, and lumbar lesions, ejaculation has occurred in 54%, 67%, and 33%, respectively, and pregnancies have resulted in 37% of couples attempting conception, apparently unrelated to the length of time since injury or the age of the men. Although the semen produced may be normal in volume and sperm count, sperm motility rarely exceeds 10% to 20%. The poor quality of the semen requires semen processing and a multidisciplinary approach to treating both the husband and wife to optimize the outcome. Although labor-intensive, electroejaculation has resulted in promising fertility alternatives for the estimated 250,000 spinal-cord-injured men in the United States today.

Epididymal sperm recovery. Some conditions are not amenable to conventional surgical techniques, such as obstructive azoospermia due to a congenital bilateral absence of the vas deferens or to severe damage to the reproductive ducts. To treat these patients, surgeons have devised reservoirs (artificial spermatoceles) to collect spermatozoa—vein grafts, woven grafts, and alloplastic spermatoceles—to be used for artificial insemination. The resultant pregnancy rate—4/91, or 4%—is reportedly low, however, owing to a failure to maintain epididymal patency and to the extremely poor motility of the collected spermatozoa. An alternative treatment method for obstructive azoospermia is in vitro fertilization. Pregnancies have occurred with the microsurgical aspiration of sperm from the head or body of the epididymis. Sperm have been adequate in number but low in motility (10% to 20%), and, although pregnancy has been reported to occur, more than 20 subsequent attempts have resulted in failure (S. J. Silber, MD, Chief of Urology, St Luke's Hospital, St Louis, oral communication, January 1988). This technique looks promising, although improved techniques to enhance the motility of the collected sperm should ultimately yield better results.

Diagnostic Advances

Whereas assisted reproductive techniques offer new hope for the treatment of male infertility, innovative diagnostic methods are now elucidating more of the causes of idiopathic infertility. With the proper diagnosis, more conventional and successful forms of therapy can be offered.

Sperm Antibodies

Immunobead binding assay. Sperm antibodies are thought to play a role in the pathogenesis of about 10% to 20% of cases of unexplained infertility. Until recently, reproductive laboratories attempting to diagnose immunities to spermatozoa used one of several major forms of serologic testing: sperm agglutination, complement-dependent sperm immobilization, and indirect immunofluorescence. These tests were subject to a number of pitfalls, and it was not uncommon to find a positive result in serum of fertile men and women. The immunobead binding tests have recently been developed to detect the presence of immunoglobulins on the surface of motile spermatozoa. The assay can be used either as a "direct" test for detecting immunoglobulins already bound to the patient's spermatozoa or as an "indirect" test for evaluating antibodies in the circulation or reproductive fluids. The immunobead binding assay can determine not only the isotype of the immunoglobulin found—IgA, IgG, or IgM—and the percentage of sperm bound with antibodies but also the region of sperm to which specific antibodies are bound. The significance of this lies in the fact that antibodies bound to different areas of the sperm affect different sperm functions such as motility, survival, and fertilization. The immunobead binding test is one of the most informative and specific of all assays currently available for detecting clinically significant antisperm antibodies. With the accurate detection of antibodies, the proper immunosuppressive therapy, although still controversial, can be given.

Varicoceles

Ultrasonography. The varicocele, a dilation of the pampiniform plexus in the internal spermatic vein, is now well established as the most commonly diagnosed cause of male infertility, and varicocelectomy is the most common surgical therapy. Clinical and laboratory studies have provided evidence that varicoceles are detrimental to spermatogenesis in some men and that this effect may be unrelated to their size. Thus, physicians have used diagnostic techniques other than the physical examination to find small but clinically important varicoceles. These include the Doppler pencil-probe stethoscope, scrotal thermography, radioisotopic angiography, and, more recently, scrotal ultrasonography. Scrotal sonography is particularly useful because it detects intrascrotal abnormalities and has a unique ability to visualize the testicle and surrounding vascular structures.

Venography. Although venography is the most specific method of identifying scrotal varicosities, it is not done routinely as it is invasive, carries some morbidity, and is expensive. The addition to venography of percutaneous techniques to occlude the varicocele—sclerothermy, detachable balloons, and coils—by interventional radiologists is an innovative method of diagnosing and treating recurrent varicoceles or as an initial option for a patient who prefers nonsurgical therapy.

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Health Care Delivery

The Malpractice Claims Experience of Physicians Investigated for Inappropriate Prescribing

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Inappropriate prescribing of controlled substances, primarily opiates and benzodiazepines, is the most common complaint brought before the Oregon Board of Medical Examiners. We describe the malpractice claims experience of 120 physicians previously investigated by the Oregon board for inappropriate prescribing. These physicians were matched with a comparison group by age, specialty, and practice location. We found that a mean of one malpractice claim had been filed against each physician in our study, with the specialties of obstetrics and gynecology, neurosurgery, and orthopedics having the most claims. A significantly higher mean number of malpractice claims had been filed against 31 physicians disciplined by the board. Our study suggests a role for state regulatory boards in the malpractice area. We propose that such bodies do practice reviews based on the convergence of two events, a disciplinary action such as those described in this article and the filing of more than one malpractice claim against a physician. Further research is needed on inappropriate prescribing by physicians and its possible association with malpractice.

(Bloom JD, Williams MH, Kofoed L, et al: The malpractice claims experience of physicians investigated for inappropriate prescribing. West J Med 1989 Sep; 151:336-338)

Of the forces reshaping contemporary medicine, certainly none are more powerful than the current malpractice "crisis." From several state legislatures to the Congress of the United States, issues surrounding escalating malpractice premiums are hotly debated. Whether the primary causes of escalating premiums are a lawsuit-conscious public fanned by an oversupply of trial lawyers or an avaricious insurance industry (or both) or by more incompetent physicians than physicians' groups care to admit, premiums continue to rise at alarming rates.[1]

It is important that physicians participate in all aspects of the debate and especially in those concerning physician competence. Physician-dominated regulatory boards are under increasing pressure to monitor more vigorously the clinical practice of physicians under their purview. These pressures are being felt in all sectors of medicine, from local hospital committees to agencies with statewide responsibilities such as boards of medical examiners. The Oregon Board of Medical Examiners (BME) is one of the more active state regulatory boards, recently ranked sixth by the Federation of State Medical Boards in the number of disciplinary actions taken by state boards per 1,000 physicians.[2] Until recently the Oregon board did little about the malpractice problem. Most of its monitoring efforts had dealt with recognizing and rehabilitating impaired physicians[3,4] and creating a program for physicians who prescribe controlled substances inappropriately.[5] Since 1978, insurance companies underwriting liability insurance in Oregon have been required to notify the Oregon BME of malpractice claims filed against Oregon physicians. In 1986 the BME hired a staff physician to examine all claims reviewed to date. Based on the initial review, physicians with four or more claims (n=100) were investigated in greater detail. Of this group, ten were felt to have practice problems that might have contributed to their malpractice claims.[6] Each of the ten physicians was interviewed, and each agreed to modify some of his or her practice. As a result of this initial project, the Oregon BME now does practice reviews on all physicians with three malpractice claims.

No clear data exist on the link, if any, between incompetent care, physician impairment, and malpractice claims. The American College of Surgeons asserts that incompetent care represents substantially less than 25% of malpractice cases.[7] Although it may be tempting to infer a relation between incompetence and malpractice claims,[8] data are lacking.

Our study grew out of a larger one[5] designed to examine characteristics of a group of physicians referred to the Oregon BME from 1981 through 1986 for possibly inappropriate prescribing. Inappropriate prescription writing was the most frequent complaint investigated by the BME, accounting for 51% of the 300 complaints investigated. The study focused on the overprescribing of scheduled drugs, mainly opiates and to a lesser degree benzodiazepines. In the present study, we investigated the relationship between inappropriate prescribing and malpractice claims. Although the literature is tentative, there seems to be an association between inappropriate prescribing, age, practice setting, and

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keeping current in medicine.[9-11] These findings point to the need for the investigation of a possible link between physicians who prescribe inappropriately and those who experience malpractice actions.

Methods

From 1981 through 1986 the board investigated 130 physicians for complaints of inappropriate prescription writing. In a section of the Oregon statutes setting out the grounds for suspending, revoking, or refusing to grant a medical license, inappropriate prescribing is defined as "Prescribing controlled substances without a legitimate medical purpose and without following accepted procedures for examination of patients and record keeping."[12] This definition covers three important areas: a legitimate purpose for prescribing, examination of the patient, and record keeping and is used by both the investigative committee and the full board to judge allegations brought against physicians.

We attempted to match each physician in this group with a noninvestigated physician. Physicians were matched for specialty, degree (MD or DO), sex, Oregon county of practice, and year of medical school graduation. An exact match was required for specialty, degree, and sex. If the county of practice could not be matched exactly, a physician from a county of similar size and location was chosen. The year of medical school graduation was matched within three years. A sample of 120 pairs of physicians was generated.

Demographic information was collected for the comparison sample from the computerized data base maintained by the Oregon BME. Malpractice claims records filed with the board were reviewed for each physician in the study. As noted, since 1978 Oregon law has required insurance carriers writing insurance in Oregon to report to the BME any malpractice claims filed against an insured physician. Claims against physicians insured by non-Oregon companies would not appear in our sample. We assumed that underreporting in the sample would apply equally to both study and comparison groups.

Results

The 120 matched pairs of physicians produced a sample in which the mean age was 53, a mean of 26 years had passed since medical school graduation, and a mean of 22 years since Oregon licensure. Table 1 presents a breakdown of the physicians' medical specialties and the percentage of each practicing in Oregon. Of the study group, 64% were involved in primary care specialties of family practice (33%), general practice (18%), and internal medicine (13%), but only 33% of physicians in practice in Oregon are in primary care.

Table 2 shows the malpractice claims data for both study-group and comparison-group physicians accused of inappropriate prescribing. Of the study-group physicians, 53% had at least one previous malpractice claim. Of comparison physicians, 44% had previous malpractice claims. These differences were not significant (paired t test, $t = 1.32$, $df = 119$, $P = .19$).

Table 3 shows the combined malpractice claims data for both the study and comparison groups presented by medical specialty and by number of claims and mean number of claims per practice category. The most frequently sued physicians are those practicing obstetrics and gynecology, followed closely by neurosurgeons and orthopedists, and then by general surgeons and family practitioners.

TABLE 1.—*Specialties of the Oregon Board of Medical Examiners Sample (n=120) and Comparison Sample (n=120)*

Specialty	Physicians in Each Sample, No.	%	% of Oregon Physicians
Family practice	40	33	13
General practice	21	18	5
Internal medicine	15	13	15
Orthopedic surgery	9	8	5
Psychiatry	6	5	5
General surgery	4	3	6
Gastroenterology	3	2	0.9
Neurology	3	2	2
Neurologic surgery	3	2	1
Obstetrics and gynecology	3	2	5
Otolaryngology	3	2	2
Cardiology	2	2	1
Pediatrics	2	2	6
Anesthesiology	1	1	5
Endocrinology	1	1	0.3
Physical medicine and rehabilitation	1	1	0.5
Emergency medicine	1	1	4
Rheumatology	1	1	0.4
Urology	1	1	2

TABLE 2.—*Number of Malpractice Claims*

Number of Previous Claims	Oregon Board of Medical Examiners Group (n=120) No.	(%)*	Comparison Group (n=120) No.	(%)*
0	57	(48)	67	(56)
1	33	(28)	32	(27)
2	18	(15)	10	(8)
3	5	(4)	9	(8)
4	4	(3)	2	(2)
5	3	(3)	0	
Mean	1.0		0.7	
Standard deviation	1.4		1.0	

*Percentages total more than 100% because of the rounding off of numbers.

TABLE 3.—*Malpractice Claims by Specialty*

	No. of Physicians (n=240)	No. of Claims (n=207)	Mean No. of Claims
Family practice	80	78	0.98
General practice	42	28	0.67
Internal medicine	30	13	0.43
Orthopedic surgery	18	35	1.94
Psychiatry	12	0	0.00
General surgery	8	11	1.38
Gastroenterology	6	4	0.67
Neurology	6	2	0.33
Neurologic surgery	6	12	2.00
Obstetrics and gynecology	6	13	2.17
Otolaryngology	6	5	0.83
Cardiology	4	2	0.50
Pediatrics	4	2	0.50
Anesthesiology	2	0	0.00
Endocrinology	2	0	0.00
Physical medicine and rehabilitation	2	0	0.00
Emergency medicine	2	0	0.00
Rheumatology	2	2	1.00
Urology	2	0	0.00

Of the 120 physicians investigated for inappropriate prescribing, 71 (59%) had their cases closed at the investigative committee level. Of these, 24 (34%) were sent a letter of concern regarding their practices, but their cases were not deemed serious enough for future consideration by the full board. The other 49 cases (41%) were sent on to the full board. We found no significant differences in the number of malpractice claims of the study and comparison groups when we compared physicians whose cases were closed at the investigative committee level with those sent on to the full board (2-factor analysis of variance).

Of the 49 cases sent to the full board, 31 had their prescribing privileges limited. These physicians agreed to give up their privilege to prescribe schedule II, III, and IV drugs. When we compared the malpractice claims experience of this group of 31 disciplined physicians with their matched comparisons, we did find a significant difference in the number of claims. The 31 physicians in the study group had a mean of 1.2 malpractice claims compared with 0.6 for their matched physicians (paired t test, $t = 2.21$, $df = 30$, $P = .035$).

Discussion

Our study is a preliminary investigation of the malpractice claims experience of a group of Oregon physicians who were brought to the attention of the Oregon BME for suspected inappropriate prescribing of controlled substances and a comparison of this group with a matched comparison group.

With 53% of the study group and 44% of the comparison group having at least one malpractice claim, we concluded that all physicians are vulnerable to suit. Because only Oregon underwriters are required by law to report malpractice claims to the BME, malpractice claims for both the study and comparison groups are underreported. For example, most psychiatrists receive their malpractice coverage through nationally sponsored policies. Although psychiatrists are not frequently sued,[13] we did have 12 psychiatrists in the study with no malpractice claims reported to the Oregon BME.

The malpractice findings also mirror national trends in those branches of medicine most vulnerable to lawsuit. Although the study group is heavily dominated by primary care physicians, those practicing obstetrics and gynecology, neurosurgery, and orthopedics have the highest number of malpractice claims filed against them.

We did find a significant difference in the mean number of malpractice claims filed against the 31 physicians disciplined for inappropriate prescribing (1.2 claims per physician) and their matched physician controls (0.6 per physician). These findings are consistent with a view of inappropriate prescribers as a potential group of high-risk physicians[14] worthy of more intensive study and possible remediation.

Our data do not help determine the percentage of malpractice claims that are actually cases of malpractice, representations of incompetence, or both. They do suggest, however, that the Oregon board's policy of reviewing a physician's practice after a certain number of malpractice claims could be beneficial and that there is value in doing more comprehensive practice reviews when two events converge, a disciplinary action for inappropriate prescribing coupled with the existence of malpractice claims. Such practice review may allow for an earlier identification of physicians at risk for practice problems and may improve the chances of discovering problems with physicians practicing in specialties at a lower risk for malpractice claims. Simply using the number of claims filed against a physician without a disciplinary action discriminates against the high-risk specialists who are more likely to experience malpractice suits.

Our study results point to a role for a regulatory body such as the Oregon BME in the malpractice arena. Clearly more research is needed in this area. Will our findings hold up after further examination or with more complete malpractice data? Do the same trends exist in relation to impaired physicians? We are currently investigating these questions and urge others to do the same, as these are areas of major importance. With medicine's house more in order, we will be freer to help bring about other needed reforms in the malpractice area.

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Environmental Health

Potential Adverse Health Effects of Wood Smoke

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The use of wood stoves has increased greatly in the past decade, causing concern in many communities about the health effects of wood smoke. Wood smoke is known to contain such compounds as carbon monoxide, nitrogen oxides, sulfur oxides, aldehydes, polycyclic aromatic hydrocarbons, and fine respirable particulate matter. All of these have been shown to cause deleterious physiologic responses in laboratory studies in humans. Some compounds found in wood smoke—benzo[a]pyrene and formaldehyde—are possible human carcinogens. Fine particulate matter has been associated with decreased pulmonary function in children and with increased chronic lung disease in Nepal, where exposure to very high amounts of wood smoke occurs in residences. Wood smoke fumes, taken from both outdoor and indoor samples, have shown mutagenic activity in short-term bioassay tests. Because of the potential health effects of wood smoke, exposure to this source of air pollution should be minimal.

(Pierson WE, Koenig JQ, Bardana EJ Jr: Potential adverse health effects of wood smoke. West J Med 1989 Sep; 151:339-342)

Homeowners have turned to the use of wood as a heating fuel because of the increasing cost of oil and natural gas. This trend has been especially striking in the northeastern and northwestern United States.[1] The Washington State Department of Ecology estimated in a study in 1984 that wood was burned in 60% of Washington households, with about 2.2 million cords of wood consumed per year. Several studies have shown the potential for wood-burning stoves and fireplaces to pollute indoor as well as outdoor air. Although wood-burning stoves and fireplaces are vented to the outside, many circumstances facilitate the access of combustion products into the indoors, including improper installation, such as insufficient stack height, cracks, leaks in or poor fitting of the stovepipe, negative air pressure indoors, downdrafts, and accidents, such as wood spilling from the fireplace.[1] Also, about 70% of the outdoor wood smoke reenters the house (T. V. Larson, PhD, University of Washington, Department of Civil Engineering, unpublished data). Combustion products of wood are highly irritating to the eyes, nose, and respiratory system. Duncan and co-workers have developed data on the types of pollutants associated with wood burning (Table 1).[2]

A wood-burning stove functions differently than a fireplace. In a fireplace, as much as 90% of a fire's heat is lost up the chimney along with exhaust gases. With a stove, the air supply is controlled and the rate of combustion is also controlled so that as much as 60% of the heat produced can be delivered indoors.[3]

Sexton and associates compared particle mass, size distribution, and chemical composition of indoor and outdoor air in a residential neighborhood.[4] They found that indoor concentrations of particles were often higher than outdoor, and although wood smoke contributed greatly to the mass, other sources also were important. They also found great variation among residences in the same neighborhood.

Traynor and colleagues measured indoor air pollution and found that both airtight and nonairtight stoves produced measurable particulate matter and polycyclic aromatic hydrocarbons within the home.[5] Nonairtight stoves emitted as much as 650 μg per m^3 for a 24-hour period. Polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, are also expelled into the indoor environment. Benzo[*a*]pyrene is a known carcinogen, and any exposure above local background levels should be avoided when possible. Other pollutants can cause both acute and toxic adverse health effects. Thus, it seems appropriate to highlight our understanding of the toxic exposures involved.

Effects of Individual Pollutants

Carbon Monoxide

Carbon monoxide is one of the most ubiquitous indoor pollutants. It is a major product of tobacco combustion, and concentrations from 2 to 110 ppm have been measured in dwellings, depending on the size of the space, the number and type of tobacco products smoked, and the adequacy of ventilation.[6] An indoor level of no higher than 5 ppm has been recommended by the American Society for Heating, Refrigeration, and Air Conditioning Engineers (ASHRAE). Incomplete combustion in fuel-rich flames due to wood burning also can produce substantial amounts of carbon monoxide, an odorless, colorless gas that has the potential to be an invisible and silent hazard. Carbon monoxide competes with oxygen on the hemoglobin molecule, forming carboxyhemoglobin. The current outdoor standard is 9 ppm for an eight-hour period, or 35 ppm for any given hour. Research on persons with coronary artery disease has shown that the amount of exercise that could be done before an attack of angina was notably shortened after carbon monoxide exposure.[7]

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Nitrogen Oxides

Nitrogen is capable of forming several types of gaseous oxides. Nitric oxide and nitrogen dioxide are found in very hot wood combustion flames, and both are toxic.[8(p103)] Nitrous oxide is not formed in normal combustion. Nitric oxide and nitrogen dioxide result from the oxygen-rich combustion of wood, coal, natural gas, or oil in a variety of stoves. These gases are very reactive and can interconvert. Nitric oxide binds to hemoglobin to produce methemoglobin. Many of the adverse effects attributed to carbon monoxide in the past may be related to the combined effect of carboxyhemoglobin and methemoglobin.[1] An indoor level of no higher than 2.5 ppm has been recommended by ASHRAE. The National Ambient Air Quality Standard for nitrogen dioxide set by the Environmental Protection Agency is 0.05 ppm averaged over one year. Nitrogen oxides may produce hematologic aberrations, affect the activity of several enzyme systems, and may also cause vascular membrane injury and leakage leading to edema. Exposures to nitrogen dioxide have been associated with toxicologic effects including pulmonary edema, bronchoconstriction, and increased infection rates. An indoor level of no higher than 0.5 ppm has been recommended by ASHRAE. Some epidemiologic evidence indicates that an increased prevalence of respiratory tract infections in young children and adult men as well as lower pulmonary function performance are associated with a history of exposure to gas stove emissions.[9] Consistent lung effects in children due to nitrogen dioxide exposure have been difficult to characterize, however.[9]

Sulfur Oxides

Sulfur dioxide is a common air pollutant from wood-burning stoves that has known airway irritating effects. Kerosene heaters have been shown to emit sulfur dioxide levels that can exceed certain occupational health standards. An indoor level of not greater than 0.5 ppm has been recommended by ASHRAE. Koenig and co-workers[10-12] have shown that adolescent subjects with asthma or exercise-induced bronchospasm or both experience large changes in pulmonary function after exposure to either 1.0 or 0.5 ppm sulfur dioxide during moderate exercise. Symptoms related to lower airway dysfunction such as dyspnea and chest tightness are generally confined to those with asthma, but healthy subjects usually complain of an unusual taste or odor.

Aldehydes

Formaldehyde is ubiquitous in our environment, and the primary indoor source of this and other aldehydes is the combustion of tobacco products. Polyurea foam insulation, particle board, and other construction products also can release formaldehyde into the indoor environment. The indoor levels reported with wood-burning stoves range from 0.3 to 1.0 ppm. The Department of Housing and Urban Development has recommended indoor levels not higher than 0.4 ppm, but ASHRAE has recommended 0.1 ppm. Formaldehyde is associated with an annoying odor and at higher concentrations—generally more than 0.8 ppm—can produce a transient irritation of the eyes and mucous membranes of the upper respiratory tract.[13] It is so soluble and rapidly metabolized that it rarely reaches the lower respiratory tract to inflict damage, except when inhaled in cigarette smoke. Formaldehyde may, on rare occasions, induce bronchial asthma at relatively high exposure doses. It appears to be carcinogenic at exceptionally high cumulative doses in rodents, but there are no conclusive studies proving its carcinogenic effects in humans.

TABLE 1.—*Emissions From Residential Wood-Fired Stoves**

Pollutant	*Emission Range, lb/cord*†
Particulates	3-93
SO_x	0.5-1.5
NO_x	0.7-2.6
Hydrocarbons	1-146
Carbon monoxide	300-1,220
Polycyclic organic materials	0.6-1.22
Formaldehyde	0.3-1.0
Acetaldehyde	0.1-0.3
Phenols	0.3-8
Acetic acid	5-48

*Adapted from Duncan et al.[2]
†The factor used to convert 1 lb per ton was 1.65 lb per cord.

Polycyclic Aromatic Hydrocarbons

Incompletely burned hydrocarbons from wood stoves are frequently found in indoor air. Usually they are all the gaseous or vaporizable hydrocarbons, such as hydrocarbons with 1 to 16 carbon atoms. Toxic hydrocarbons are produced if plastic materials are incinerated in wood stoves. Resulting polycyclic aromatic hydrocarbons have been shown to be carcinogenic in animal studies. Coke oven workers have exposure to polycyclic aromatic hydrocarbons in levels similar to those measured in wood smoke fumes; these hydrocarbons can serve as a surrogate for wood smoke exposure. Studies have shown that coke oven workers with 15 years' or more exposure have a 16-fold excess risk of having lung cancer as compared with the general population.[14] One of the polycyclic aromatic hydrocarbon compounds, benzo[*a*]pyrene, is a proven carcinogen in animals.

Effects of Pollutant Mixtures

Most experimental studies, because of experimental design constraints, investigate the health effects of exposure to only one agent at a time. In real life, however, people are exposed to many pollutants. The effect of the described pollutants in combination with one another is reason for additional concern. Only a few studies have been conducted with wood smoke itself. One has investigated the incidence of respiratory illness among 31 preschool children living in homes heated with wood-burning stoves as compared with 31 children living in homes heated by other means.[15] Moderate to severe respiratory symptoms such as wheezing and cough at night were notably greater in the wood stove group compared with the control group. Possible confounding factors were investigated. Approximately the same proportion of children in each group had exposure to parental cigarette smoking in the home. There was no significant difference between groups in terms of the presence of urea formaldehyde insulation or the use of humidifiers. On the other hand, another study with older children—kindergarten through sixth grade—indicated that having a wood stove in the home did not increase significantly the frequency of acute respiratory episodes.[16] In this study formaldehyde exposure, estimated from construction or remodeling products, showed a small association with respiratory symptoms. Controlling for wood stove use did not diminish the formaldehyde effect.

Epidemiologic studies of long-term exposure to wood smoke have found an increased prevalence of respiratory illness in both children and adults. A study by Anderson[17] suggested an association between wood smoke exposure and chronic lung disease in adults in Papua New Guinea. Another study with children in the same region found no difference dependent on exposure except for an excess of wheeze in boys.[18] In a study in the hill region of Nepal the prevalence of chronic bronchitis among nonsmoking women increased substantially with the duration of time per day spent near the fireplace.[19] Houses there are poorly ventilated and have no chimneys. The absence of chronic bronchitis in men was suggested to be due to the lesser amount of time they spent indoors with the burning wood.

A unique case was reported of a 61-year-old woman who had shortness of breath. She was evaluated for interstitial lung disease of an unknown cause. Bronchoalveolar lavage revealed the presence of numerous particles and fibers that were identified as wood. The patient lived in a home heated with a solid-fuel radiant room heater that roasted wood to produce heat.[20]

A review of the health effects of indoor air pollution in general with some mention of wood smoke was published in 1987.[9] Also in 1987, Dockery and colleagues[21] concluded that wood stove use was associated with an increased relative risk for respiratory illness in children selected from grades 2 through 5 in six cities where wood stove use ranged from 46% to 5%. The odds ratio was 1.32 (95% confidence intervals 0.99 to 1.76).

Particulate Matter

Wood stoves have been shown to emit substantial amounts of fine particulate matter of less than 10 μm in size. Fine particulate matter ranging in size from 0.02 to 10 μm is of concern to public health because it has been shown to be readily inspired and deposited into lungs. The finest particles are deposited more deeply in lungs where some can remain indefinitely and cause morphologic and biochemical changes.

In a study in Steubenville, Ohio, decreases in lung function in children correlated with elevated concentrations of total suspended particulate matter.[22] In a similar study in the Netherlands, lung function measurements were followed in 179 children aged 7 to 11 years during a winter season in which total suspended particulate matter was being monitored and 3% to 5% reductions in lung volume measurement were found during air pollution episodes when high concentrations of particulate matter were present.[23] Taken together, these studies suggest that declines in lung function associated with episodic exposures to total suspended particulates occur rapidly and persist for as long as two to three weeks before recovery. Particles of less than 10 μm were measured during the winter of 1985-1986 in Olympia, Washington. For a period of five days, the concentration was greater than 150 μg per m^3. Wood smoke concentration was high and responsible for 80% to 90% of the fine particles. For comparison, the concentration at the same sampling site during the summer of 1986 was approximately 20 μg per m^3.

Airborne wood smoke fumes, collected both inside and outside homes using wood stoves, have been analyzed for their toxic properties. Kamens and associates[24] have shown that wood smoke fumes contain mutagens according to the Ames short-term mutagenicity assay. The volatile organic compounds, polycyclic aromatic hydrocarbons, and especially semivolatile compounds all showed mutagenic activity, with some having as much as 100 times the activity of some well-known carcinogens. Alfheim and co-workers showed that the polar fraction of organic extracts from emissions of wood combustion had direct mutagenic activity in a modified Ames *Salmonella* assay.[25] Using another test of mutagenicity, sister chromatid exchange, Hytonen and colleagues showed the capacity of emission from an airtight residential wood stove to induce sister chromatid exchange.[26] Burnet and Insley reported that emissions from both traditional and advanced technology wood stoves caused sister chromatid exchange in mammalian cells.[27] Even though the newer stoves produced less particulate matter and carbon monoxide, the emissions from these stoves did give a positive response to the sister chromatid exchange test. In another study, air samples were collected from occupied homes using wood as an energy source and mutagenic activity was found in the air of 8 of the 12 homes sampled.[28]

Other Combustion Sources of Indoor Pollution

Whenever unvented combustion takes place indoors or venting systems attached to stoves, boilers, or heaters are malfunctioning, a wide variety of combustion products can be emitted directly indoors. Besides tobacco combustion, the primary sources of combustion by-products in residential buildings are usually space heaters, gas stoves, and gas water heaters, as well as wood stoves. Exhaust from automobiles in homes with attached carports or garages and oil and kerosene lamps and candles can be additional sources of combustion by-products.

Summary

Concern over the quality of outdoor air has been an active issue in the United States for many years. A substantial portion of the Environmental Protection Agency's budget of $300 million is devoted to concern about the contamination of our outdoor environment, such as the selenium contamination of water in California, acid rain in the Great Lakes, or a toxic waste dump in New York.[29] Though these are important issues, most people spend 80% to 90% of their time indoors, each taking well over 10,000 breaths per day to provide the necessary oxygen for human metabolism. More time is spent indoors in the harsh winter months.

The increasing use of wood as a heating fuel has precipitated concern for its potential to further pollute the outdoors but, perhaps more important, to contaminate the home. Many irritating and potentially carcinogenic compounds have been identified in wood smoke, including carbon monoxide, nitrogen and sulfur oxides, fine particulate matter, and various aromatic hydrocarbons, including benzo[*a*]pyrene. In addition to wood smoke, various other combustion sources have been identified that could directly augment the problem. Several studies have identified dozens of toxic chemicals that all appear to originate in common household activities and practices in homes.

With respect to burning wood, it is advised as well that only dry, cured wood—less than 20% water content—be burned because combustion will be more complete and fewer products of incomplete combustion will be released into the air. All stoves should be operated in a manner to produce efficient burning with minimum smoke emissions. It is important to emphasize that even the newest airtight wood

stoves emit a considerable amount of fine particles to the outdoor air.[26] Plastic and other synthetic products should never be incinerated in wood stoves. We also strongly recommend curtailing all indoor wood burning during air pollution episodes or stagnations. Finally, we propose that public health authorities increase their research and monitoring efforts directed at this important issue.

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Radiologic Case

An 80-Year-Old Man With Acute Abdominal Pain

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

An 80-year-old man presented with an acute onset of cramping upper abdominal pain, nausea, and vomiting. He had had no previous operations. On physical examination the abdomen was distended and nontender with hypoactive bowel sounds. A plain film of the abdomen was taken immediately (Figure 1) and another one 4 hours later (Figure 2).

What is the diagnosis?

What test would you do next?

SEE FOLLOWING PAGE
FOR DIAGNOSIS AND DISCUSSION

Figure 1.—An upright film of the abdomen taken on admission shows a dilated loop of small bowel in the left upper quadrant and gas and fecal material in the colon.

Figure 2.—A second upright film of the abdomen taken 4 hours later shows a change in the gas pattern in the distal bowel.

(Patanella L, Davies S, Stegman CJ, et al: An 80-year-old man with acute abdominal pain. West J Med 1989 Sep; 151:343-344)

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DIAGNOSIS: Small bowel obstruction due to midgut volvulus

THE INITIAL PLAIN FILM of the abdomen (Figure 1) shows a single loop of dilated small bowel in the left upper quadrant. There is gas and fecal material in the colon. On the film taken four hours later (Figure 2), there is no significant change in the dilated loop, but the distal bowel gas pattern has changed. In adynamic ileus, both large and small bowel loops are usually dilated, and the gas pattern remains relatively stable over time. The findings, therefore, suggest an obstructing lesion in the proximal small bowel, but this is not an unequivocal picture. Other causes of proximal small bowel dilatation such as pancreatitis can produce the same changes. Because of this, an upper gastrointestinal tract examination with small bowel follow-through was done.

The upper gastrointestinal tract examination (Figure 3) shows an abrupt change in caliber in the proximal jejunum. The most common cause of this appearance is obstruction due to adhesions from a surgical procedure. Because this man had not had a previous operation, other causes of small bowel obstruction were considered. A large air-filled jejunal diverticulum was present just distal to the area of narrowing, and a review of the plain films showed that this had been present on all previous examinations. During surgery, the small bowel was seen twisted around the large diverticulum. The volvulus and diverticulum were resected, and the patient recovered.

Figure 3.—An early film from a small bowel examination shows a narrowed segment of jejunum **(arrows)** and a large, air-containing diverticulum distal to the narrowing **(arrowheads).**

Volvulus is defined as a loop of intestine that has twisted 180 degrees or more on itself, resulting in obstruction of the loop. There is often associated compromise of the vascular supply to the involved loop. A small bowel volvulus can be primary (rare) or secondary to many other factors (usual). Predisposing conditions include malrotation, congenital bands, postoperative adhesions, tumor, intussusception, or internal hernia. It is important to diagnose the condition early because mortality rates as high as 67% have been reported with delay in treatment. Morbidity and mortality result from vascular compromise with ischemia and necrosis of the bowel.

Presenting symptoms of small bowel obstruction due to any cause include cramping and intermittent pain, vomiting, abdominal distension, and decreased bowel sounds. These signs are nonspecific and often lead to a delay in treatment when many other (nonsurgical) causes of abdominal pain are being considered.

Radiographic signs of small bowel obstruction are unequivocal in about a third of patients. In the other two thirds, barium examinations are often required to establish the diagnosis. In the past there has been some reluctance to use barium in patients with a possible small bowel obstruction, but this reluctance is unfounded. The only contraindications to small bowel barium studies are possible perforation and colonic obstruction. The use of a water-soluble medium is often less rewarding because mixing of the contrast with fluid in the bowel makes a diagnosis less certain.

A small bowel volvulus produces a characteristic whorl-like pattern on a computed tomographic scan, with mesenteric vessels in a circular pattern in the preaortic region. On angiography, the same spiral pattern may be seen, along with delayed or absent filling of small bowel vessels due to the vascular obstruction. These more intensive examinations are seldom needed, however, as the diagnosis can be made on plain films and a barium examination in the great majority of patients.

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Public Health and Preventive Medicine

Death Certification

Purposes, Procedures, and Pitfalls

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Completing a death certificate properly and promptly is an important duty for physicians, who must understand how the death certificate is used and be able to recognize and employ the concepts of immediate, underlying, and contributing causes of death. Accurate, concise terminology should be used to give in a logical order a sequence of events leading to death. Avoiding mistakes in death certification helps reduce potential medicolegal problems and provides more meaningful statistics for health care personnel.

(Klatt EC, Noguchi TT: Death certification—Purposes, procedures, and pitfalls. West J Med 1989 Sep; 151:345-347)

It is important for physicians to understand how to complete a death certificate properly. The accurate completion of this legal document is necessary for the needs of registrars compiling health statistics, persons engaged in medicolegal work, hospital or other health care personnel, and the family of the deceased. Prompt completion is necessary to ensure that funeral arrangements proceed without delay because burial cannot take place without a properly signed death certificate. The death certificate is a public document that can be obtained by the deceased person's family, researchers, insurance companies, attorneys, or other litigating parties. Physicians must bear in mind that the certificate may be reviewed by others and that inconsistencies or inaccuracies may be noticed.

It is the responsibility of the physician who cared for a deceased person to fill out this certificate unless the death comes under the jurisdiction of a medical examiner or coroner. An inappropriately or carelessly worded death certificate may be rejected by the official public registrar of vital statistics for the jurisdiction (usually county) with whom these certificates are filed, causing delays and possibly inducing unwanted litigation. Further difficulties may stem from ramifications regarding the cause of death—such as with asbestosis—and insurance or Workers' Compensation benefits, the physician's loss of rapport with family members, and questions regarding the physician's judgment. Proper death certification is also important for the compilation of health statistics,[1,2] on which allocations of private and governmental health care resources may be made.[3]

The death certificate must document the cause of death—a condition, event, or disease process incompatible with the continuation of life.[4] It is not concerned with the mechanism of death—often a physiologic event such as cardiac or respiratory failure—which does not explain why the death occurred. Terms such as "cardiopulmonary arrest," "respiratory failure," or "old age" should never be used. These are not causes, but manifestations, of death. Physicians should not be concerned with the manner of death—that is, natural, accident, homicide, suicide, or undetermined. The responsibility for investigating the circumstances under which death occurred to determine the manner of death lies with the medical examiner (coroner).[5]

The principal reasons for death certification, as defined by governmental agencies with the legal power to enforce and regulate it, are for use as the official public documentation of death and for the compilation of statistical information by cause of death for public health agencies. This certificate is not intended as a detailed medical record for discussing a deceased's history or clinical problems; rather, it focuses on a single underlying cause of death, as determined by the responsible physician.

Often physicians have no clear idea why death occurred at a particular time. A dramatic event causing death may have taken place but usually did not. Patients may linger on through an extended clinical course, at least partially responding to treatment. A patient's appearance on the day of death may not differ significantly from that on previous days. Another problem in determining the cause of death may be a lack of sufficient findings, especially when patients die suddenly or soon after admission to a hospital.

If obvious or dramatic events or fully documented conditions leading to death are lacking, the physician should determine what conditions are known from the admitting diagnosis or problem list.[6] The death certificate need not contain a dramatic finding. In fact, the principal underlying cause of death in the United States remains atherosclerosis, primarily occurring as coronary artery disease or cerebrovascular disease (stroke). Neither atherosclerosis nor the second most

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common cause of death, neoplasia, always leads to a rapid demise.

There is a national standard for basic statistical data, but each state may require additional information on the death certificate. Some states have a separate certificate for fetal deaths. Differences among the states involve mainly the recording of demographic data. The US standard form on which most state death certificates are patterned was revised in January 1989. The cause of death portion of this new form, shown in Figure 1, differs from most current certificates in that an additional line has been provided for listing causes of death and more explicit instructions are given. It is hoped that the adoption of this new standard in future revisions of state death certificates will lead to greater accuracy.

For most of the current death certificates, as many as three lines may be used to list the cause of death, and there is an additional line for contributing cause(s). All lines need not be used. Never use abbreviations, such as SLE (systemic lupus erythematosus) or AIDS (acquired immunodeficiency syndrome), but spell out all terms completely. The interval between when the listed condition began and the time of death need not be exact but may be estimated in relative terms such as minutes, hours, days, months, or years. Indeterminable intervals may be listed as "unknown." Often the interval can be stated exactly, as in death from myocardial rupture four days after a myocardial infarction.

The single disease process initiating the sequence of events that culminated in death is the underlying cause of death. That is, had this process not occurred, the patient would most likely still be alive.[7] It is perfectly reasonable in some cases to give just the underlying cause without listing a poorly understood chain of consequences. Some examples of one-line death certificates (with intervals) are ruptured intracerebral artery aneurysm (minutes), meningococcal septicemia (hours), multiple congenital anomalies (2 days), adenocarcinoma of pancreas with metastases (1 year), intrauterine fetal demise (at birth), or marked pulmonary emphysema (years). Only in the first example did a single, dramatic event occur that caused death. In the other examples, death due to the underlying condition resulted from mechanisms that were complex, poorly understood, or both. Elucidating these mechanisms is not necessary because the underlying condition alone was sufficient cause for death.

In many cases, when the events leading to death are known, the physician uses more than one line and gives a so-called immediate cause of death—an event that immediately preceded death but had an underlying cause.[7] Two immediate causes—three with the new US standard—may be given. In general, if the underlying cause can lead to death through a variety of means (for example, diabetes mellitus may lead to infection or atherosclerosis in more than one organ), then immediate causes of death should be listed. The last line, however, must still state the underlying cause that led to other events and that must have been present at least as long as the other events. It is this last line on which most statistics are based. Findings should be listed in a logical sequence of a clinical course. Not all intermediate steps can be listed, just the most important ones.

Examples of the proper use of the immediate cause of death (with intervals) include the following: acute myocardial infarction (2 days) due to coronary artery thrombosis (2 days) due to severe coronary atherosclerosis (years); *Pneumocystis carinii* pneumonia (3 days) due to acquired immunodeficiency syndrome (unknown); congestive cardiomyopathy (months) due to hypertension (years); bleeding esophageal varices (9 hours) due to micronodular cirrhosis of

Cause of Death
The cause of death means the disease, abnormality, injury, or poisoning that caused the death, not the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure

In Part I the immediate cause of death is reported on line (a). Antecedent conditions, if any, which gave rise to the cause are reported on lines (b), (c), and (d). The underlying cause should be reported on the last line used in Part I. No entry is necessary on lines (b), (c), and (d) if the immediate cause of death on line (a) describes completely the train of events. ONLY ONE CAUSE SHOULD BE ENTERED ON A LINE. Provide the best estimate of the interval between the onset of each condition and death. Do not leave the interval blank; if unknown, so specify.

In Part II enter other important diseases or conditions that may have contributed to death but did not result in the underlying cause of death given in Part I.

PART I. Enter the diseases, injuries, or complications that caused the death. Do not enter the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure. List only one cause on each line.		Approximate Interval Between Onset and Death
IMMEDIATE CAUSE (Final disease or condition resulting in death)	a. Bronchopneumonia	1 week
	DUE TO (OR AS A CONSEQUENCE OF):	
	b. Atherosclerotic heart disease	years
Sequentially list conditions, if any, leading to immediate cause. Enter UNDERLYING CAUSE (Disease or injury that initiated events resulting in death) LAST	DUE TO (OR AS A CONSEQUENCE OF):	
	c.	
	DUE TO (OR AS A CONSEQUENCE OF):	
	d.	

PART II. Other significant conditions contributing to death but not resulting in the underlying cause given in Part I	WAS AN AUTOPSY PERFORMED (Yes or no)	WERE AUTOPSY FINDINGS AVAILABLE PRIOR TO COMPLETION OF CAUSE OF DEATH? (Yes or no)
Chronic obstructive pulmonary disease	yes	yes

Figure 1.—The figure shows the cause of death portion and instructions of the United States standard death certificate form adopted January 1989. Individual state certificates vary primarily in the number and placement of demographic items.

the liver (years) due to chronic alcoholism (years); and chronic renal failure (years) due to chronic glomerulonephritis (years). In states adopting the new standard form (Figure 1), a more complex chain of events can be listed, such as aortic dissection (minutes) due to hypertension (years) due to chronic renal disease (years) due to scleroderma (years).

When disease processes or events were present that were unrelated to the underlying cause of death but that made death more likely, they may be listed as "other conditions." Because only one underlying cause of death can be listed, coequal or near-equal conditions to that cause may be listed as another condition contributing to death.[8] The "other conditions" line, however, is not to be used just to continue a problem list for the patient but rather to state significant conditions that hastened demise from the underlying cause. Illustrative examples (with intervals) include the following:

- Small-cell anaplastic carcinoma of lung (6 months), with other significant conditions including diabetes mellitus or atherosclerotic heart disease.
- Disseminated candidiasis (1 week), due to diabetes mellitus (years), with other significant conditions including adenocarcinoma of prostate.
- Hypernatremia (1 day) due to acute viral gastroenteritis (2 days), with other significant conditions including congenital heart disease.

Never use the line for other conditions for the underlying cause of death. For example, thrombosis of a mitral valve prosthesis followed by rheumatic heart disease as another condition would be incorrect because rheumatic heart disease caused the chain of events leading to mitral valve replacement. Do not use the line for other conditions merely to modify or explain the cause of death and put unnecessary lines in the death certificate. Contributing causes of death should be unrelated to the underlying cause. For instance, a cause of death given as infiltrating ductal carcinoma of breast, followed by a mastectomy as another condition, is incorrect because mastectomy was a mode of treatment and did not make death more likely. Operations or treatments should be listed only if they were directly involved in the sequence of events leading to death, as in aplastic anemia (2 months) due to an idiosyncratic reaction to carbamazepine therapy for seizure disorder (two months).

The events listed in a death certificate do not necessarily have to occur close together. The underlying condition may have been present for years or may have occurred years ago. Pulmonary emphysema of 2 years' duration, for example, may be due to cystic fibrosis of 18 years' duration. Some conditions traditionally cannot be one-line causes of death. These include most acute inflammatory processes such as pneumonia and pancreatitis that usually do not occur de novo. In cases of chronic debilitation, such underlying conditions could include senile dementia or other chronic processes as in bronchopneumonia (2 weeks) due to Alzheimer's disease (years).

Death certificate information must be in a proper sequence. For example, "prematurity" would not logically precede "hyaline membrane disease" but should follow it. Sometimes physicians mistakenly list the underlying problem first, then other conditions, as in a problem list. Such mistakes are inexcusable and would serve to discredit a physician's expertise for all other entries in the medical record.

The terms "possible" or "rule out" should not be used. The term "probable" may be applied when diagnoses have not been completely established before death. Another common error is to list "aspiration" when it is an agonal event rather than an unexpected cause (accident). Unnecessarily listing an event associated with an accidental manner of death prompts a coroner's review and promotes speculation concerning patient management. Likewise, circumstances associated with suicide, homicide, or an undetermined manner of death come under the medical examiner's jurisdiction.

The best way to compose a death certificate is to think in terms of disease processes that brought about death. Without an autopsy, a physician must rely on the history and the results of the physical examination and radiologic or laboratory procedures to provide the data that determine what process led to death. Was it a neoplasm, infection, congenital condition, or other disease state? What part of the body was affected? What was the sequence of events? It is best to be succinct and to refrain from providing a multitude of terms, hoping that one applies.

Physicians should not hesitate to list conditions that failed to respond to treatment. Accuracy is essential for risk management, for the medical record may be reviewed.[9] Not every patient responds to therapy, nor is it necessary to include a complication of treatment in the death certificate. For example, a patient may die during bronchoscopy, but if death was a known possibility (complication) or an agonal event due to a serious underlying disease, then it is not an accident. Pulmonary embolus is a complication of some patients in hospital but is not considered an accident.

Deaths from therapeutic misadventure are considered accidents only if the misadventure was part of the sequence of events leading to death. If the terminal event was an expected risk of a diagnostic or therapeutic procedure, the manner of death would be natural. A blatant, obvious, or gross error or mistake made during a diagnostic or therapeutic procedure that led to death would be considered a therapeutic accident.

Contrary to the opinion of some physicians, we have found that an autopsy or clinical record, including the death certificate, that documents unexpected or undesirable findings does more to reduce medical malpractice problems than does a poorly documented clinical course. Uncertainties or inaccuracies can lead to unwanted or untrue speculations. The use of common sense, good judgment, and concise terms that follow a logical sequence of events facilitates accurate death certification.

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Information

A Travelers' Clinic in an Academic Setting

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The Department of Family and Community Medicine at the University of Arizona has operated a travelers' clinic since 1983, staffed primarily by faculty and residents from the sections of preventive medicine, occupational medicine, and family medicine. We describe the clinic experience in providing preventive medical services to international travelers. Summer months are the busiest. Destinations of the travelers show a clear predominance of travel to less-developed countries, and this is reflected in the immunizations and prescriptions provided. After their trips, travelers reported a low incidence of diarrhea of generally low severity. The travelers' clinic is also a positive experience for resident physicians who help staff it, particularly those specializing in general preventive medicine.

(Cordes DH, Baca CT, Grant KJ: A travelers' clinic in an academic setting. West J Med 1989 Sep; 151:348-351)

The travelers' clinic at the University of Arizona Health Sciences Center has been a clinical preventive medicine activity of the Environmental Preventive Occupational Health Clinic since late 1983. The concept of a separate and organized clinical activity in this area originated with the preventive medicine residency director, and the clinic was initially largely established by a resident in occupational medicine. The travelers' clinic staff assesses the health risks of persons who are about to embark on international travel. Emporiatric services including preventive counseling, prescriptions, and all necessary immunizations are provided. (Emporiatrics is the science of the health of travelers visiting foreign countries.) Oral and written instructions are provided concerning health hazards in the countries to be visited. Under faculty supervision, resident physicians assume administrative responsibility for the travelers' clinic and provide medical services. All travelers' clinic patients are seen initially by preventive and occupational medicine residents who staff the clinic four to eight hours weekly throughout their residency. Attending physicians are available for immediate consultation.

In this article we describe our experience in providing preventive medicine services to travelers. We also report the results of a survey of resident physicians in preventive and occupational medicine who have worked at the clinic.

Patients and Methods

We initially collected data on all patient encounters at the travelers' clinic on a month-by-month basis from October 1983 to March 1987. Intake charts were reviewed for all travelers who visited the clinic during 1986, and the following were recorded: sex, age, destination, immunizations provided, prescriptions for malaria medications, duration of travel, purpose of travel, and interval between first clinic visit and departure. All patients seen in 1986 were surveyed to determine if any had become ill during their travels or were delayed at international borders because of a lack of medical documentation. The survey specifically asked about symptoms of diarrhea, fever, nausea, and vomiting. Travelers were also queried regarding other illnesses suffered during their travels. There was no attempt to contact, for purposes of comparison, other university- and community-based travelers using other sources of pretravel advice and health care.

An additional survey was done of all present and past occupational and preventive medicine residents (1983 to 1987) to determine whether they had found working in the travelers' clinic enjoyable, educational, and applicable to their present or future careers.

Results

A total of 551 visits were represented. The data show an increase in the number of patients seen. There was also definite seasonal variation in 1984 and 1986, with a peak during the summer months.

An analysis was made of all patient visits during 1986. A total of 114 travelers were seen in 280 clinic visits; 58 (51%) were female and 56 (49%) were male. Their ages ranged from 15 to 74 years with a mean of 41.2 years.

The primary destinations by continent were as follows: 43% traveled to Asia, primarily to India, China, or Thailand; 25% traveled to Latin America; 43% had African destinations; and 4% were going to Europe. The mean number of countries visited was 2.35: 51% went to a single destination, and the rest visited as many as 11 countries. Most stays in each country were brief. Most (83%) travelers planned on staying less than a month, usually one to two weeks; a smaller group (4%) planned on staying six months or longer.

The time between the first clinic visit and travel was calculated and is presented in Figure 1. Most (66%) travelers did not provide us the recommended six weeks before travel.[1]

In response to a query on the major reason for travel, respondents indicated pleasure (47%) slightly more often than job-related activities (42%). About 9% were traveling for educational purposes, and 2% were visiting relatives.

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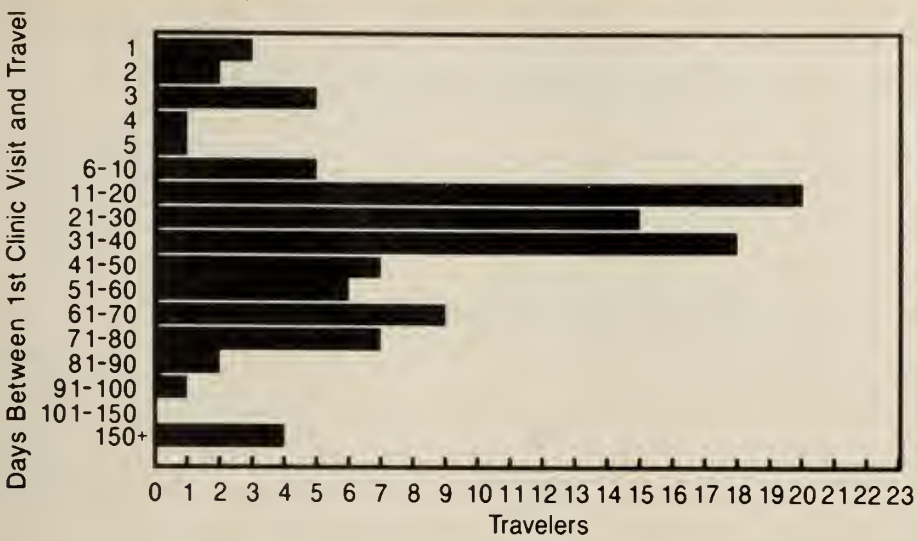

Figure 1.—The graph shows the timing of clinic visits before travel.

Women were twice as likely to travel for pleasure, and men were more likely to be in job-related activities involving foreign travel. Persons involved in job-related travel tended to be slightly younger (mean 40.0 years) than those traveling for pleasure (mean 46.1 years).

The frequency of various types of immunizations provided travelers is shown in Table 1. The data reflect the high percentage of travel to underdeveloped areas. Immune serum globulin to protect against hepatitis A was the most commonly provided immunization, given to 86% of travelers. Polio vaccine was provided in accordance with Centers for Disease Control guidelines[2] to the 67% of our travelers with destinations where poliomyelitis was epidemic or endemic. Of the 76 poliovirus immunizations, 46 were oral and 30 were inactivated. Tetanus and diphtheria toxoids were given to 42%. The frequent necessity for yellow fever vaccine (42%) reflected the percentage of travel to tropical areas of Africa and South America. Typhoid vaccine was given to 54%, along with verbal and written advice about food and water precautions. Cholera vaccine was usually given only to travelers visiting countries where it was required by immigration authorities before entry after travel to an endemic area. Additionally, Japanese B encephalitis immunization was provided to 20 travelers during the last three months of 1986.

Malaria medications were also frequently prescribed. Chloroquine phosphate was prescribed to 84%, and 30% traveled to chloroquine-resistant areas and received prescriptions for the combination of sulfadoxine and pyrimethamine in addition to chloroquine. Of these patients, 3% were allergic to sulfonamides and so were given doxycycline. Only 13% were going to areas where no malaria prophylaxis was needed.

TABLE 1.—*Immunizations Provided Prospective Travelers (n=114)*

Immunization	*Travelers* No.	*Travelers* %
Immune serum globulin	98	86
Tetanus and diphtheria toxoids adsorbed (adult)	48	42
Poliovirus vaccine	76	67
Yellow fever	47	41
Typhoid fever	61	54
Cholera	32	28

Questionnaires were sent to all travelers whose records were examined—that is, to all seen in our clinic in 1986. A 70% return was obtained. Fortunately, no one was held up at international borders for a lack of medical documentation. Nearly 13% experienced diarrhea, defined as a twofold or greater frequency of bowel movements when the nature of the stools is watery during travel. Of those with diarrhea, 50% had it for one day, 25% for two days, and none had it for longer than a week. One person had nausea and vomiting lasting a few hours. Two travelers had fever due to upper respiratory tract infections that cleared within two days.

Of the 20 residents who had participated in the clinic, 19 responded to the survey. Eleven had been preventive medicine residents and eight occupational medicine residents. Results of the survey are shown in Figure 2. The resident physicians had found working in this activity both enjoyable and educational. In general, however, the occupational medicine residents felt that their experience in the travelers' clinic was less applicable to their present or future careers. Preventive medicine residents were generally more satisfied.

Discussion

As noted above, summer months have been the busiest, except for the summer of 1985. This slowdown was perhaps due to the rash of attacks on foreign airlines and airports that had recently occurred. In July 1985 few international travelers were seen compared with the other years in which July was the busiest month. Thus, international events may have a profound effect on the practice of emporiatrics.

The slight predominance of women visiting the clinic is consistent with the slight predominance of women who obtain US passports. In 1984, for example, 2,595,000 of the 4,718,000 (55%) passports issued were to women.[3(p236)] The mean age of 41.2 years for travelers seen at the clinic reflects the fact that children younger than 16 years are not routinely seen.

The destinations of travelers who visited the clinic showed a clear predominance of travel to less-developed countries. In comparison, 1983 statistics for all US and Puerto Rican residents traveling overseas show that nearly half (49%) go to European or Mediterranean countries, only

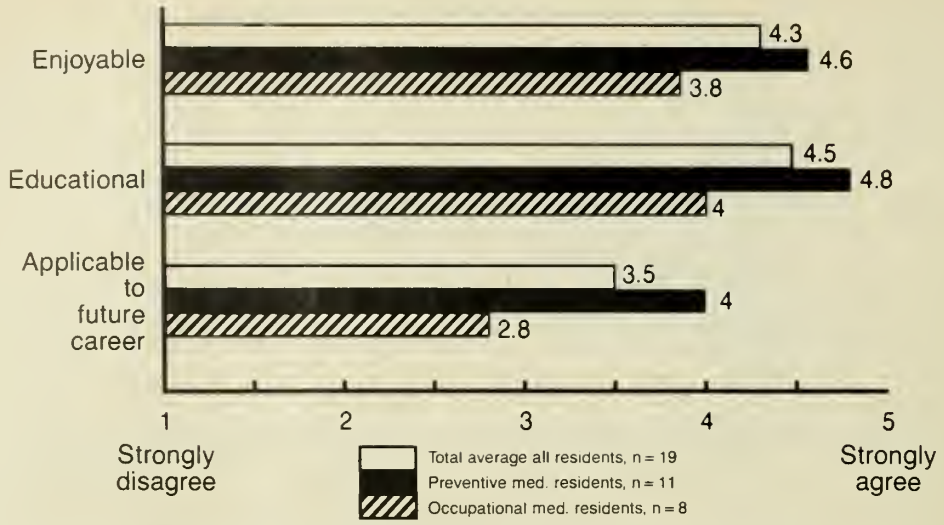

Figure 2.—Resident physicians' (n = 19) satisfaction with their experiences in the travelers' clinic is shown in the graph. The bars indicate the means of responses for each group.

14% to African or Asian destinations, and less than 6% to South America.[3(p237)] The difference presumably reflects the basic reasons people visit a travelers' clinic: to obtain prescriptions for malaria prophylaxis and immunizations for diseases common in tropical countries (typhoid fever, cholera, yellow fever, hepatitis, poliomyelitis, and Japanese B encephalitis).

The short interval between the first visit and departure has been a problem. Emporiatric planning should begin with risk assessment at least six weeks before departure.[1] Several immunizations, including those for cholera, Japanese B encephalitis, typhoid, rabies, and plague, require a series of injections over time. Too often travelers do not visit early enough to allow the time needed for immunizations. Sometimes it is necessary to arrange for vaccines to be administered during actual travel. These suboptimal arrangements would not be necessary if travelers allowed six weeks before travel. As providers of travelers' health care, we must inform future travelers of the importance of timing travel clinic visits.

The travelers' clinic not only provides immunizations to protect travelers against numerous tropical diseases but also provides an additional service by attempting to ensure that all are up to date in routine immunizations against tetanus, diphtheria, and poliomyelitis.

Tetanus remains a significant health risk. Between 1982 and 1984, there were 253 cases of tetanus reported in the United States.[4] Of these, 96% were in persons older than 20 years, and more than 70% were in persons older than 50. A study of urban adults in Minnesota showed that most women older than 40 years and men older than 60 did not have protective levels of tetanus antitoxin.[5] Thus, it is imperative that appropriate immunization be given if more than ten years have elapsed since the last booster.

The same Minnesota study showed that only 23% of adults had protective levels of diphtheria antitoxin. It is therefore recommended that diphtheria toxoid be given in combination with tetanus toxoid. This has been the practice at the clinic.

Although polio booster immunizations are not currently recommended for adults residing in the United States, many international travelers have destinations in endemic areas where they will be at risk of contracting polio. These patients were given a polio booster if they had not had polio immunization since childhood.

The circumstances of the patients in our study were such that none required immunizations against measles, hepatitis B, rabies, or plague. Some patients under certain circumstances may require these, however, which adds to the complexity of providing emporiatric care.[2]

The large number of persons who received immunizations against yellow fever, typhoid, cholera, or Japanese B encephalitis and the vast majority who received immune serum globulin reflect the predominance of travelers with destinations in underdeveloped nations. Decisions regarding when and to whom to administer these vaccinations are also complex.[2]

Malaria also remains a serious health risk to travelers. There were 1,941 cases of malaria in US civilian overseas travelers between 1970 and 1980.[6] Because there is as yet no effective vaccine against malaria, preventive drug therapy must be used. The problem of which medications to prescribe to which patients requires advanced emporiatric skills. Destinations, duration of stay, the type of accommodations and location (urban versus rural), the prevalence of chloroquine-resistant strains, and patient allergies must all be considered.[2]

In addition to providing an important service, the travelers' clinic has also proved to be a positive experience for the resident physicians staffing it, particularly those specializing in general preventive medicine. Experience in emporiatrics may be especially helpful to those specializing in family practice, internal medicine, or pediatrics because personal physicians are frequently consulted by patients before international travel.[7] Some additional guidance for practitioners is available in recent literature.[8-10]

International travel has become a major factor in modern life. Currently, 15 to 20 million people travel from industrialized to developing nations each year.[11] In addition to this group of mostly tourists and business people, there is a large group of immigrants, refugees, and migrant laborers. An important challenge for all in emporiatrics in the future is to address the needs of travelers such as refugees and migrant farm workers as well as tourists and business persons.

Because of the great need, emporiatrics is emerging as a new medical specialty, with many new travelers' clinics being established.[12]

Our approach to emporiatrics is to tailor prophylactic treatment specific to an individual itinerary and to attempt to modify behavior through education to prevent disease in travelers. It is hoped that this article will be helpful for others in establishing similar activities.

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Rocky Mountain Spotted Fever

IN RECENT YEARS, we have begun to see more Rocky Mountain spotted fever. A tick bite will be seen in about 60% of these patients. Fever and headache will be the primary symptoms in most. Headache alone may be the primary symptom in a few. Most are diagnosed as having viral infections, fever of unknown origin, or measles. When they are put into hospital—most are in hospital for about nine or ten days—the diagnosis is not often made until several days into the hospital stay.

The accompanying rash is more subtle than one thinks. There is a far more intense rash on the extremities. There is not much in the way of coalescence, as one might expect with a measles rash, and although there is some rash on the trunk, it is not nearly as prolific. It tends to be far more concentrated, and it will start—if you get a good history—it will almost always start along the distal extremities and then progress to the trunk. The treatment for Rocky Mountain spotted fever is chloramphenicol. There really is no particular substitute. Tetracycline hydrochloride is probably also effective and may be used in patients who are really intolerant of chloramphenicol.

—GARY D. OVERTURF, MD

Extracted from *Audio-Digest Emergency Medicine,* Vol. 6, Issue 12, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Information

Injuries to Search and Rescue Volunteers

A 30-Year Experience

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Tucson

SEARCH AND RESCUE is a vital component of a rural and wilderness emergency medical system. Yet it differs from the normal component of the emergency medical system in the complex logistics often needed to effect a rescue, the often hostile environment in which teams operate, and the unique physical conditioning and training needed by rescue personnel.

To a limited extent, injuries and illnesses requiring intervention by wilderness search and rescue personnel have been documented.[1,2] Little is known, however, about the injuries sustained during both operations and training by search and rescue personnel themselves. To learn more about such injuries, a local search and rescue operation was studied. The Southern Arizona Rescue Association (SARA) is a completely volunteer search and rescue organization that has been operating, at the request of local law enforcement, forest service, and fire department officials, in southern Arizona for 30 years. Its scope of activity includes mountain and desert searches, technical rescues and evacuations, cave and mine rescues, and river rescues. Averaging 60 to 80 operations a year, field time for personnel during operations approximates 110,000 hours over the organization's 30-year existence. An additional 30,000 hours have been spent in field training. The organization consistently has between 40 and 60 men and women actively involved at any one time. The average age of members is 31 years, with a minimum age of 16 years.[3]

Methods

Injuries or acute illnesses in the field that required a physician's attention or evacuation of SARA rescue personnel were culled both from available organizational and governmental records and from the memories of members who have been active throughout the organization's existence. These three sources were used to cross-check the validity and completeness of the data. The time lost from field activities, if rescue personnel needed to leave the field, plus time lost from work because of injuries, were totaled. The total time members of this rescue organization have spent in the field during the organization's existence was extrapolated to full-time-equivalent positions as is done for other job classifications by the United States Occupational Safety and Health Administration.[4]

(Iserson KV: Injuries to search and rescue volunteers—A 30-year experience. West J Med 1989 Sep; 151:352-353)

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Results

Musculoskeletal injuries were the most common type of injury that SARA members suffered over the years (Table 1). These included two fractures, a disrupted knee, a shoulder dislocation, and sprains requiring emergency department evaluation. There were many more minor sprains and strains for which no assistance was needed. This category included the only injuries for which time was lost from work or rescues.

Other injuries and illnesses included one near drowning (evaluated and released from the emergency department), one case of hypothermia, a scorpion sting, a chipped tooth, and an acute exacerbation of multiple sclerosis. There were numerous close encounters with cactus, although these never required medical care. There were no deaths. The time lost from field activities, if rescue personnel needed to leave the field, plus time lost from work because of injuries totaled 360 hours. The calculated rate of lost workday injuries for SARA members over its 30-year existence can be extrapolated to 60 days per year per 100 full-time-equivalent workers.

Discussion

The rate of lost workday injuries experienced by Southern Arizona Rescue Association members is similar to the 63 lost workdays per year per 100 full-time workers found in health service personnel and notably less than the 117 lost workdays per year per 100 full-time fire service personnel (Table 2).[4]

TABLE 1.—*Injuries to Search and Rescue Volunteers**

Musculoskeletal	*Other Injuries*
Tibiofibular fracture†	Finger laceration
Knee disruption†	Chipped tooth
Finger fracture	Scorpion sting
Shoulder dislocation	Near drowning
Ankle sprain	Hypothermia
Knee sprain	*Illnesses*
	Multiple sclerosis

*All injuries listed occurred once.
†Lost workday injuries.

TABLE 2.—*Comparison of Lost Workdays by Occupation*

Occupation	*Lost Workdays per Year per 100 Full-time Personnel**
Mining	145
Construction	129
Fire protection	117†
Transportation, public services	107
Agriculture, forestry, fishing	91
Manufacturing	80
Health services	63
SARA members	60
Wholesale, retail trade	51
Finance, insurance, real estate	15
Legal services	7

SARA=Southern Arizona Rescue Association

*1985 statistics rounded to nearest whole number (from Bowman[1]).
†Extrapolated from other information.

It is difficult to directly extrapolate the SARA experience with the injuries of team members in other search-and-rescue groups. There are several reasons for this. First, each search-and-rescue organization operates within a unique environment and organizational structure. The Southern Arizona Rescue Association operates in a setting where about 70% of the calls are in a relatively warm or hot environment. Many of its evacuations are on scree slopes—loose rocky debris—rather than solid rock, and more than half of the operations take place partially or completely after dark. Field operations are organized under a modification of the Incident Command System used by the US Forest Service.[5] Second, the sheer amount of activity of this volunteer group, as well as the longevity of its members—the average length of service of active members is eight years—gives SARA operations, in many respects, a more professional than volunteer appearance. Third, an ingrained part of training and operations is that the safety of rescue personnel comes first. This is constantly emphasized and is routinely reinforced during operations, postoperation debriefings, and formal group discussions of operations.[6] Finally, helicopters are only rarely used to transport SARA personnel. Most operations are conducted on foot.

Search and rescue is undoubtedly an exciting part of the emergency medical system. Yet the experience of the Southern Arizona Rescue Association suggests that volunteer search-and-rescue activities, while continuing to be effective, need not be unusually dangerous.

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2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

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4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

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Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics It must be considered in differential diagnosis of antibiotic-associated diarrhea Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms
- Positive direct Coombs' tests have been reported during treatment with cephalosporins
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include.
- Gastrointestinal (mostly diarrhea): 2 5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever). 1 5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported
- Other: eosinophilia, 2%, genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis, elevations in BUN or serum creatinine
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly) [061088L]

Additional information available from Eli Lilly and Company, Indianapolis, Indiana 46285 PV 2351 AMP

Lilly **Eli Lilly Industries, Inc**
Carolina, Puerto Rico 00630

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CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* statewide. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy three physician Family Practice group (including OB) seeks replacement for partner departing fall 1989. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

INTERNAL MEDICINE, NORTHERN CALIFORNIA. You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. All subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Christy Jensen or Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

BAY SHORES MEDICAL GROUP

offers an outstanding opportunity for a BC/BE Cardiologist with invasive and interventional expertise. We are an 80-physician multispecialty group practice in southern California, close to ocean, easy access to city and recreational areas, excellent schools. Please direct any inquiries and CV to Bradford B. Burnett, MD, Medical Director, Bay Shores Medical Group, Inc, 3625 Del Amo Blvd, Ste #270, Torrance, CA 90503; (213) 543-7247.

PHYSICIANS WANTED

ASSISTANT MEDICAL DIRECTOR/SUPERVISING PHYSICIAN SPECIALIST

Laguna Honda Hospital, an 1,100-bed city and county skilled nursing facility with acute care, rehabilitation, and hospice services, seeks a BC physician with program planning, administrative, and clinical experience to direct several expanding clinical services. Must be able to perform needs assessments, design and implement new services, and work with the city budget and personnel system as well as with multidisciplinary teams and community agencies. A strong clinical background with an interest in teaching is essential.

This position requires an enthusiastic physician dedicated to improving health care for a medically underserved group of predominantly elderly and newly disabled patients.

Salary range is $72,254-$87,828 depending on experience and qualifications. This civil service position includes an excellent benefits package.

Interested individuals may submit résumés to:

Mary Anne Johnson, MD
Medical Director
Laguna Honda Hospital
375 Laguna Honda Blvd
San Francisco, CA 94116

(415) 664-1656

An Equal Opportunity Employer

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

IDAHO. Opportunity for high quality of life, low cost of living in beautiful Idaho—sunbelt of the Pacific northwest. Join Family Practice teams at one of six multi-site community/migrant health centers providing primary care to rural communities. Outstanding four-season recreation, malpractice insurance paid, generous continuing education, competitive salary and benefits, loan repayment potential, and opportunity to provide OB services. Send résumé to Dean Hungerford, Idaho Primary Care Association, PO Box 6756, Boise, ID 83707; or call (208) 345-2335.

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

(Continued on Page 358)

AIM HIGH

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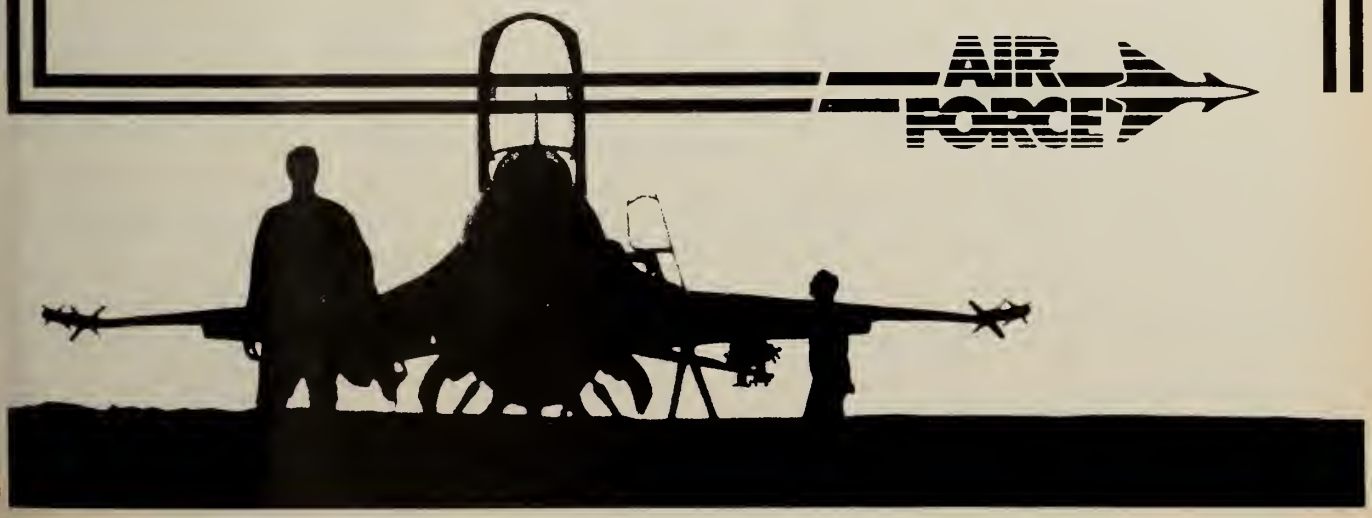

(Continued from Page 356)

PHYSICIANS WANTED

GENERAL SURGEON. Established young, mellow but compulsive General Surgeon in southern California seeks an associate so he can spend more time with his young children. If interested send CV and personal description to Number 159, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful ambulatory health care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE primary care specialists preferred. Contact Bob Morris, MD, FACEP, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294, or 1 (800) 234-1231.

PEDIATRICIAN. BC/BE physician to join seven member Pediatric department in 55 physician multispecialty group. New medical building with inhouse ancillary services, urgent care center, and surgery center. Competitive salary, excellent benefits including partnership opportunity. Please send CV or contact Susan Smit, Director, Practice Development, Harriman Jones Medical Group, 2600 Redondo Ave, Long Beach, CA 90806; (213) 988-7062.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, General Surgery, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

OREGON

Excellent opportunity for BC/BE General Internist with large multispecialty group in Portland metropolitan area. Group provides comprehensive medical care to 350,000 members of established northwest HMO. Position offers wide range of Internal Medicine and ample opportunity for subspecialty consultation within collegial professional environment. Competitive salary and benefit package, including generous pension program, sabbatical leave, and professional liability coverage. Forward inquiry and CV to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227

PHYSICIANS WANTED

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy	OB/GYN
Cardiology	Orthopaedics
Dermatology	Otolaryngology
Family Practice	Urgent Care
General and Vascular Surgery	Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

LOOKING FOR INTERNIST/FAMILY PRACTITIONER to join five physician group in Truckee, California. Northern Sierras at elevation 6,000 feet. Abundant recreation summer and winter—beautiful Lake Tahoe, restaurants, and skiing. 40-bed hospital with six ICU beds. Contact R. B. Ganong, MD, PO Box 2649, Olympic Valley, CA 95730; (916) 583-5320.

PSYCHIATRIST

BC/BE, part-time, possibly developing to full-time. Expanding San Francisco bay area practice emphasizing Occupational Medicine and med-legal evaluation seeks consulting Psychiatrist. Outstanding reputation, facilities and support staff, established referral base. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
Box 337
San Francisco, CA 94109

Ads Get Results!

UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is in the second phase of an ambitious development plan and is searching for physicians residency trained in Emergency Medicine. The Health Sciences campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level I trauma center, has paramedic base station training responsibilities, and has a helicopter service. Emergency Physicians supervise medical students, interns, and residents in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

SOUTHERN CALIFORNIA

Dynamic, multispecialty group is seeking Specialists and Primary Care Physicians for our facilities in Los Angeles and Orange Counties. Excellent compensation and benefit package. Please send CV to:

Robert Harrington, MD
CIGNA Healthplans of CA
505 N. Brand Blvd, #400-49
Glendale, CA 91203
or call collect (818) 500-6570

(Continued on Page 359)

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PHYSICIANS WANTED

BC/BE INTERNIST being recruited for the community of Artesia, New Mexico. Solo practice with cross-coverage available from local Internist. Community-based financial assistance may be available for the right individual. Family oriented community with year round recreation; excellent weather. Fully equipped 38-bed hospital. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

PATHOLOGIST. AP-CP to join three BC AP-CP with special competence, certified in Dermatopathology, Immunohematology, and Immunopathology. 300-bed progressive acute care hospital. Adding a fourth Pathologist due to workload. Must have or be willing to develop a forté in Microbiology in addition to sharing AP workload. State-of-the-art medicine. All medical and surgical subspecialties represented. Boise, Idaho's capital city, has an enviable four season climate with abundant recreational outlets. World class fine arts center. Four year college with large stadium and sports pavilion. Downtown parks and river known for float trips and fishing. Six double chair lift skiing 16 miles away. Excellent schools. Great place to raise a family. Competitive income. Desire recently trained individual. All details first letter. No phone calls please. Reply to John C. Day, MD, 190 E. Bannock, Boise, ID 83712.

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

SACRAMENTO AMBULATORY/URGENT CARE. Part-time openings for Family Practitioners and Internists with experience in adult ambulatory care. Clinic operates 12 hours per day, seven days a week for acute care. Flexible scheduling. Benefits available for physicians working at least six half days per week on a regular basis. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

FAMILY PRACTICE, NORTHERN CALIFORNIA. Immediate opening. Competitive salary. Excellent benefits. Malpractice provided. Contact Debra Pahl, CTHP, 564 S. Dora St, Ste D, Ukiah, CA 95482; (707) 468-5341.

(Continued on Page 360)

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

MARTINEZ

Emergency Physicians — Join friendly, relaxed and highly professional colleagues at our 204-bed hospital in the heart of the San Francisco Bay Area. We are seeking experienced physicians, BE/BC preferred. Locum Tenens and part-time work available Summer/Fall, 1989 & Winter/Spring, 1990. Recent adjustments provide excellent hourly rate plus paid malpractice. Career positions also available, providing salary and excellent benefits package. Send CV to: Ted Bayer, M.D., Chief, or Andrea Wagner, M.D., Asst. Chief, Department of Emergency Services, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1000, ext. 3316 or (415) 372-1124.

Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

FAIRFIELD

Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including scheduled time off, malpractice insurance, medical, dental and life insurance, and a substantial retirement program. Our physicians are free to concentrate on providing quality health care, without the burdens of managing a practice.

To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

KAISER PERMANENTE

Good People. Good Medicine.

(Continued from Page 359)

PHYSICIANS WANTED

NORTH CENTRAL IDAHO

17 physician multispecialty group recruiting BC/BE partners.

- 2nd Dermatologist
- 2nd Gastroenterologist
- 3rd General Internist
- 6th Pediatrician

Progressive medical community. Outstanding recreational area. Excellent life-style.

Send CV to:

Bob Baker, Administrator
Valley Medical Center and Children's Clinic
2318 Vineyard Ave
Lewiston, ID 83501
(208) 746-1383

SAN FRANCISCO MEDICAL DIRECTOR AND PHYSICIANS

For establishing community clinic with ethnically diverse patients, 21,000 patient visits per year. BC/BE Family Physician for above positions. Full-time/part-time, available now. Medical directorship would include 50 percent administrative time for assistance with grants, quality assurance, etc. Academic appointment, prenatal care, and teaching opportunities. Excellent benefits, competitive salary. MPH and administrative experience preferred for Medical Director.

Send CV to: **Michael Williams, SFMCOIP, Inc, PO Box 40519, San Francisco, CA 94140.**

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Michael Getzell, MD, Chief, Dept of Internal Medicine, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545.

SAN FRANCISCO. Seeking BE/BC Internist for part-time or full-time locum tenens in busy department of medicine with full subspecialty backup. Excellent salary and full benefits if working six or more half days. California license essential. Contact Paul Feigenbaum, MD, Chief of Service, Kaiser Permanente, 2200 O'Farrell St, San Francisco, CA 94115; (415) 929-2665. EOE.

GENERAL PRACTICE—SOUTHEAST WASHINGTON. 32 physician multispecialty clinic needs full-time physician as second physician in Immediate Care Center. Center is part of main clinic and has full range of ancillary and consultative services available. Abundant free time with no on-call responsibility. Excellent school system. Outstanding recreational and cultural opportunities. Guaranteed salary with excellent fringe benefits. Contact Robert Caudill, MD, or David Maloney, Administrator, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720.

INTERNIST. BC/BE Internist wanted to join Internal Medicine group practice. Competitive salary and excellent fringe benefits. Early partnership. Send CV to Number 162, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602, or call Sara Brenner, (213) 478-5913.

PHYSICIANS WANTED

OCCUPATIONAL HEALTH MEDICINE

OGDEN, UTAH

McKay-Dee Hospital Center, located 30 miles north of Salt Lake City, is seeking a Physician to provide medical treatment for injury/illness care, and perform physical examinations in our Ogden and Salt Lake City WorkMed Clinics. Will also assist in policy and procedure development, training medical staff, and participate in sales/marketing meetings and activities as required. Assists in QA development and analysis. Internal medicine or emergency room training/experience helpful. Must be licensed physician or licensure eligible and be a graduate of an approved/accredited school of medicine. Excellent benefits and competitive salary enhance this position. Enjoy the Utah adventure...

Submit CV to : **JoLynn Richards, Human Resources Department, 3939 Harrison Boulevard, Ogden, Utah 84409. 1-801-625-2061.**

McKAY-DEE HOSPITAL CENTER

A Facility of Intermountain Health Care
An Equal Opportunity Employer M/F/H/V.

DIAGNOSTIC RADIOLOGIST to associate with six physician group at county hospital (major trauma center) and private office partnership after two years. Start early September or by arrangement. Equal Opportunity Employer. Contact L. Preger, MD, (415) 437-4205, Highland Hospital, 1411 E. 31st St, Oakland, CA 94602.

BC/BE INTERNIST being sought to establish practice in resort community of Ruidoso, New Mexico. Beautiful mountain setting with easy access to all forms of recreation. Financial assistance may be available for the right individual. For more details, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

GYNECOLOGIST needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648; (405) 225-2511.

INTERNAL MEDICINE, SEATTLE. BE/BC full-time Primary Care, to join two other Internists now. Well established growing progressive practice near major north end hospital. Income guarantee first two years. CV to Internal Medicine, 540-C NE Northgate Way, Ste 139, Seattle, WA 98125.

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

GENERAL INTERNIST/NEUROMUSCULAR/COPD / REHABILITATION. We are seeking a BC/BE General Internist to join the staff of a 48-bed respiratory unit at an internationally recognized rehabilitation center affiliated with the University of Southern California. Must demonstrate interest in management of respiratory-neuromuscular/chest wall disorders, COPD and tuberculosis. Some critical care. Busy exercise lab. Opportunity in clinical investigation. Clinical faculty appointment at USC, depending on qualifications. Interested individuals should send CV to Ahmet Baydur, MD, Chest Medicine Service, Rancho Los Amigos Medical Center, 7601 E. Imperial Hwy, Downey, CA 90242. Equal Opportunity/Affirmative Action Employer.

GENERAL INTERNIST. Group practice located in beautiful northern California wine country seeks General Internist. We are opening a new 106-bed hospital February 1990; a superb opportunity to join a growing, thriving practice. Excellent salary, benefits, security, and ample time off. Please send CVs to Richard Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

SOUTHERN CALIFORNIA

Exciting opportunity for Dermatologist to develop an interesting and challenging practice in sophisticated metropolitan Los Angeles area. Easy access to major academic centers, cultural and recreational activities. Superb salary and benefits. Send CV to:

Director/Professional Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Ste 400-49
Glendale, CA 91203
or call collect (818) 500-6236

(Continued on Page 361)

(Continued from Page 360)

PHYSICIANS WANTED

CALIFORNIA, WESTERN STATES, AND TEXAS
Opportunities for BE/BC physicians in ENT, Internal Medicine, Family, General Surgery, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and others. Phone or send CV to **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0672 or FAX (415) 376-0813.**

FAMILY PRACTITIONERS AND GENERAL INTERNISTS, Sacramento Kaiser Permanente. Must be BC/BE. Family Practitioners join 23 Family Practitioners with excellent consultant support. Internists work in established Department of Medicine, experience continuing growth. Pleasant practice setting where physicians are free to provide the highest quality medicine with full access to diagnostic and therapeutic services. Affiliated with University of California, Davis, providing a substantial part of their residency programs. Excellent financial package includes in-house CME and retirement package, with no billing or practice management headaches. To join our successful, growing medical group, Family Practitioners send CV to Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825. Internists send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

CALIFORNIA, SAN FRANCISCO BAY AREA. Saint Louise Health Center is a new hospital scheduled to start operations October 1. This is an exciting opportunity for BC/BE Emergency Physicians to organize and start-up a level II emergency service. Located in Morgan Hill, a high growth desirable residential area on the outer fringe of Silicon Valley, this position includes membership in a prestigious northern California staffing group which is democratically governed and academically oriented. Please mail CV to Kate Lawlor, Emergency Physicians' Medical Group, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected urgent care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Robert Korns, MD, 6800 Soquel Dr, Aptos, CA 95003 or call (408) 662-3611.

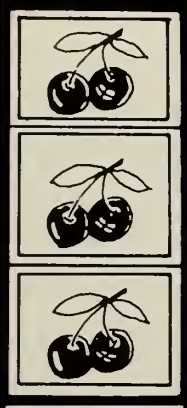
SAN FRANCISCO. Well established General Internist seeks BE/BC associate, private practice, some Geriatric emphasis, benefit package includes incentive options, pension funds, malpractice. Contact Martin Lorber, 1500 Southgate Ave, Daly City, CA 94015; (415) 992-4466.

EUGENE CLINIC, EUGENE, OREGON
Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Internal Medicine, OB/GYN, Occupational Medicine, Orthopedics, General Surgery (breast disease focus), Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

(Continued on Page 362)

ADS GET RESULTS



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Prestigious national clinic group specializing in the treatment of venous disorders seeks a highly qualified and experienced M.D. to lead our growing western region practice. We require a minimum of 15 years of teaching, clinical and administrative experience. Must have proven M.D. leadership abilities, interpersonal skills and communication skills. Fifty percent administration (travel)—50% clinical practice mix anticipated. We offer an outstanding salary and bonus potential along with full benefits.

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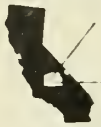
(Continued from Page 361)

PHYSICIANS WANTED



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- Orthopedic Surgeon
- Pediatrician
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Huntington Beach, CA 92647

(Continued on Page 364)

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(Continued from Page 362)

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Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

VP MEDICAL SERVICES for Medi-Cal prepaid health plan and fee-for-service community health center. Responsible for Quality Assurance, Utilization Review, provider staffing. Excellent salary and fringe benefits. California license, two years management experience in HMO setting, and formal management training. CV to President/CEO, PO Box 30051, San Jose, CA 95156-9985. EOE.

FAMILY PRACTICE, KENT, WASHINGTON. Established Family Practice clinic looking for full-time physician. Excellent salary. Production incentive available for practice builders. Partnership potential. Contact Lisa Barry at Covington Medical Clinic, 17128 SE 272nd, Kent, WA 98042; (206) 630-3100.

SEATTLE/TACOMA AREA. North Pierce/South King County area. Primary Care Physician needed for established practice. Financial assistance available. High growth area. Young families. For details, call Eloise Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70433.

SAN DIEGO. Well established, multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92018; (619) 295-0599.

ACADEMIC GENERAL INTERNIST. The University of Utah School of Medicine, Division of General Medicine is offering full-time positions for BE/BC Internists at the instructor/assistant professor/associate professor levels. Rank and salary commensurate with qualifications. Opportunities include patient care, teaching of medical students and residents, administration, and clinical research. Applications must be postmarked by October 30, 1989; applications submitted after the deadline may be considered if no qualified candidates have applied by that deadline. An Equal Opportunity Employer. Contact John H. Holbrook, MD, Dept of Internal Medicine, University Hospital 4B-120, Salt Lake City, UT 84132.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

FAMILY PRACTITIONER. Excellent opportunity in the culturally rich, 4-Corners area of northwest New Mexico. All aspects of Family Practice including prenatal. No deliveries. Outstanding benefit package. Recreational paradise in community of 30,000. Call or send CV to Sheila Brenner, Physician Recruiter, Farmington Community Health Center, PO Box 3239, Farmington, NM 87499; (505) 327-4796.

FAMILY PRACTITIONER. BC/BE to join eight member Family Practice department in multispecialty group. No OB. Near Sacramento. Send CV to Caroline Brown, MD, Dept of Family Practice, Woodland Clinic Medical Group, 1207 Fairchild Ct, Woodland, CA 95695.

CALIFORNIA. BC/BE HEMATOLOGIST/ONCOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

CALIFORNIA. BC/BE OTOLARYNGOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering either professional association or solo practice start-up. Includes attractive income guarantee. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

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of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

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OTOLARYNGOLOGY
OB/GYN
NEUROLOGY
ORTHOPEDICS
PEDIATRICS
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Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package, leading to partnership after 18 months.

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Physician Recruitment
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445 W. Eaton Ave
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BC/BE FAMILY PRACTITIONER for diverse practice in rural Minnesota. Join busy group of three Family Practitioners and replace retiring senior member. Minor Obstetrics, one in three call. Excellent quality of life in beautiful lakeside location 45 minutes from St Cloud. Competitive financial package includes guarantee plus bonus, benefits, insurance, malpractice, relocation, and all expenses. Contact Paul Clukies, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987.

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CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
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(Continued on Page 366)

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(Continued from Page 364)

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Cost Care, the nation's leading healthcare cost management company, is seeking a part-time Psychiatrist with a current California license to work within our Psychiatric/Substance Abuse Department. Ideal candidate will have:

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Send résumé/CV to:

Paul Gerhardt, PhD
COST CARE, INC
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Huntington Beach, CA 92647

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established group practice. Excellent office, lab, x-ray department. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

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SAN FRANCISCO. Outstanding opportunity for BC/BE Internist or Family Practitioner at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

ONCOLOGIST NEEDED for multispecialty group practice in Seattle; affiliated with University of Washington. Full-time clinical with potential for research. Diverse patient population includes managed care, fee-for-service, retired and active duty military. Attractive salary plus incentive and excellent benefit package. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIAN OPPORTUNITIES NATIONWIDE

For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Len Nugent and Co, 1556 Halford Ave, Ste 181, Santa Clara, CA 95051; or call (408) 984-8293, FAX # (408) 984-0412.** Never a fee to the physician.

PHYSICIANS WANTED

CHIEF OF PROFESSIONAL CLINICAL SERVICES. Official County Title: Principal Public Health Physician. Challenging opportunity for experienced physician to plan and supervise professional services in all public health clinics in Riverside County, one of the fastest growing counties in California. Salary: $58,219-$72,134 and employer paid PERS. Excellent benefits. For detailed requirements and application materials contact Riverside County Personnel Dept, 4080 Lemon St, Room 109, Riverside, CA 92501-3664; (714) 787-6125. EOE AA M/F/H.

MD TO ASSIST in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine/Emergency Room practice. Five Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. $72k per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

URGENT CARE PHYSICIAN. Full- or part-time position available paying $45 per hour. Contact Marla Antoine, (916) 423-2144.

SAN FRANCISCO BAY AREA—GENERAL INTERNIST. BC/BE General Internist needed immediately for half-time practice at the Palo Alto Medical Clinic. This is a job sharing situation with another General Internist. This is a multispecialty group affiliated with Stanford University Hospital. Please send CV to Deirdre Stegman, MD, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

PSYCHIATRIST. Full- or part-time position, innovative team working with senior citizens, med evaluations, consultations, some supervision. $300 to $600 per day. National Institute for Behavior Change, (303) 296-2244; ask for Lois Munson.

TEXAS. Very prestigious all BC group seeks an additional OB/GYN to join thriving practice near Dallas. The practice is situated in modern office building across the street from 200-bed hospital. Negotiable six-figure salary is offered with paid malpractice and other comprehensive benefits. Partnership extended at end of second year. Friendly community with historic homes. For more information call Scott Toth, 1 (800) 327-1585 or (305) 271-9213 in Florida.

GENERAL SURGEON—SAN FRANCISCO BAY AREA. Small group of well established, BC General Surgeons are now seeking to add another member with two to three years practice experience. Send CV to Manager, Professional Relations, PO Box 1438, Dept HH-9A, Louisville, KY 40201-1438; or call toll-free, 1 (800) 626-1590.

NEUROLOGIST

BC/BE, full- or part-time, for expanding San Francisco bay area private practice with emphasis on clinical Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
Box 337
San Francisco, CA 94109

PHYSICIANS WANTED

CALIFORNIA: SACRAMENTO. Director of Emergency Services in 150-bed, level II Emergency Department with 30,000 annual visits. Requires BC and significant clinical experience. Includes clinical responsibilities and administrative stipend. Exciting opportunity for membership in prestigious California Emergency Physicians group which is democratically governed and academically oriented. Send CV to Kate Lawlor, Emergency Physicians' Medical Group, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

TUCSON, ARIZONA. BC/BE, residency trained Family Physician sought to join busy solo Family Physician in private practice. Attractive start-up package available. Send CV to Herb Jalowsky, MD, 1701 W. St Mary's Rd, Tucson, AZ 85745; (602) 622-1414.

PEDIATRICIAN for State Health Division, Special Children's Clinic, Reno, Nevada. Must be BE/BC. Preference will be given to a candidate experienced in developmental pediatrics. Salary commensurate with credentials to a maximum of $80,029. Liberal benefits. Call (702) 786-0241 for further information.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural life-styles. Contact Dr Donn Cobb, Health Officer, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

PUGET SOUND. BC/BE Family Practitioner for new branch office of multispecialty clinic. Full Family Practice opportunity, OB optional. Guaranteed starting salary and benefits. Respond with CV to Memorial Clinic, Attention: Inge Hart, Personnel, 500 N. Lilly Rd, Olympia, WA 98506; (206) 456-1122, ext 249.

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SUBSTANCE ABUSE—CHEMICAL DEPENDENCE. Ten years experience including acute care and patient education. BC Internist med-eligible for AMSAOD exam. Current location, southern California. Reply to Number 167, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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BEAUTIFUL NAPA VALLEY, CALIFORNIA. Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

ORTHOPEDIC SURGERY PRACTICE FOR SALE. Ventura County, California. Well established. Retiring. Good opportunity, plus good potential for further growth. Arthroscopic surgery skill useful, but not essential. Well equipped office. X-ray. Recently redecorated. Reply to Number 164, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

GENERAL PRACTICE AVAILABLE, MENDOCINO COUNTY. MD cutting back, but will still be working. Patients accustomed to go to Emergency Room nights and weekends. Country living in beautiful valley. Reply to Number 165, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 367)

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PRACTICES AVAILABLE

NORTHERN AND CENTRAL CALIFORNIA

Established practices available: Ophthalmology, Family, Dermatology, Internal Medicine, OB/GYN, and Pediatrics. Reasonable terms and prices. Call or write **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0672.**

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SAN DIEGO. Family—OB/GYN—General and Pediatric practices available. Long established—doctors retiring. Various prices—low down payments. Call CBI, the San Diego professional practice sales specialists, (619) 283-7009.

COARSEGOLD (MADERA COUNTY). General Practice-Family Practice MD now greatly needed in Coarsegold on beautiful Yosemite Highway 41. Growing fast in Sierra foothills. Have complete MD building waiting with excellent opportunity! Building lease at $800 per month, no deposit. Center also for sale by owner. Beautiful creekside location, excellent client potential, beautiful area near Bass Lake, good air and water. Good schools, residential locations and more. Please call owner, (209) 683-2554.

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MEETINGS

SEVENTH ANNUAL ADVANCES IN HEART DISEASE
December 1-3, 1989, San Francisco, California. Fees: $350 for ACC members; $415 for non-members; $175 for residents, fellows-in-training, nurses, and technicians. 19 Category 1 credit hours. For information, call **American College of Cardiology, (800) 253-4636; in Maryland, (301) 897-5400.**

COURSES

KAUAI, HAWAII, JANUARY 20-28, 1990
TWO CONTINUING EDUCATION PROGRAMS FOR GENERALISTS AND INTERNISTS
Family Practice: Caring and Curing, January 20-25. Pain Management: Compleat Approach, January 26-28. Contact **Academy for Continuing Education of Kauai, PO Box 457, Kalaheo, HI 96741.**

ST PAUL'S HOSPITAL CME COURSE, Vancouver, November 1, 2, 3, 1989. The 35th Annual St Paul's Hospital Continuing Medical Education Course will be held at the Vancouver Convention Centre. This popular course is directed to Family Physicians in both rural and urban practices and will provide excellent speakers on Back Pain; Hyperlipidemia; Emergency; Therapeutics; AIDS; Eyes/ENT. For further information: Susan Tate-Smith, Medical Services, St Paul's Hospital, 1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada; (604) 682-2344, loc 2721.

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1990, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1990, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 14-17, 1989, Westin Hotel, Vail.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1990, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1990, date and location to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1990, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 13-15, 1989, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 28-October 1, 1989, SEATAC Red Lion, Seattle.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1990, date and location to be announced.

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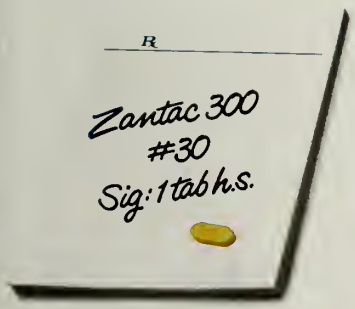

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac 300

ranitidine HCl/Glaxo 300 mg

Glaxo ROCHE

See attachment page for Brief Summary of Product Information

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60 seconds to relief...

Extended duration of action, unsurpassed bronchoselectivity*

Fast Action, Fast Relief in Asthma

Alupent®

(metaproterenol sulfate) Inhalation Aerosol

15 ml; 15 mg/ml (each metered dose delivers 0.65 mg metaproterenol sulfate)

*In controlled single-dose studies with Alupent Inhalation Aerosol, the duration of effect of two to three inhalations (20% or greater increase in FEV_1) has varied from one to five hours. In multiple-dose studies (up to q.i.d.), the duration of effect for a similar dose of Alupent has ranged from about one to two and a half hours.

Please see following page for brief summary of prescribing information

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877

Fast Action, Fast Relief in Asthma

Alupent®

(metaproterenol sulfate)

Tablets 10 and 20 mg	Inhalation Aerosol 15 ml†	Syrup 10 mg/5 ml	Inhalation Solution 5% 10 ml and 30 ml	Inhalation Solution Unit-dose Vials 0 4% and 0 6%

†15 mg/ml (each metered dose delivers 0 65 mg metaproterenol sulfate)

Brief Summary of Prescribing Information

CONTRAINDICATIONS Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated
Although rare, immediate hypersensitivity reactions can occur Therefore Alupent® (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous Fatalities have been reported following excessive use of Alupent® (metaproterenol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown Cardiac arrest was noted in several cases Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents Therefore, it is possible that this phenomenon could occur with Alupent Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol

PRECAUTIONS Because Alupent® (metaproterenol sulfate USP) is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.
Information for Patients Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent
Carcinogenesis Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility
Pregnancy *Teratogenic Effects. Pregnancy Category C.* Alupent has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose There are no adequate and well-controlled studies in pregnant women Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation
Nursing Mothers It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when Alupent is administered to a nursing woman
Pediatric Use Consult package insert for age limit

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported
The most frequent adverse reactions to Alupent® (metaproterenol sulfate USP) Inhalation Solution are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients and nausea which occurs in about 1 in 50 patients Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients

HOW SUPPLIED ***Inhalation Aerosol:*** Each canister of Alupent® (metaproterenol sulfate USP) Inhalation Aerosol contains 225 mg of metaproterenol sulfate as a micronized powder in inert propellants Alupent Inhalation Aerosol with mouthpiece (15 ml) Alupent Inhalation Aerosol refill (15 ml) Store below 77°F (25°C). Avoid excessive humidity
Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 ml or 30 ml with accompanying calibrated dropper
Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate
Alupent Inhalation Solution Unit-dose Vial is supplied as a 0 4% or 0 6% clear colorless or nearly colorless solution containing 2 5 ml with 25 vials per box Store below 77°F (25°C). Protect from light Do not use the solution if it is brown or has a precipitate
Syrup: Alupent is available as a cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 fl oz bottles Store below 86°F (30°C) Protect from light
Tablets: Alupent is supplied in two dosage strengths as scored, round white tablets in bottles of 100
Tablets of 10 mg coded BI/74 Tablets of 20 mg coded BI/72
Storage for bottles Store below 86°F (30°C) Protect from light
Storage for blister samples Store below 77°F (25°C) Protect from light

Consult package insert before prescribing.

AL-4268 AL-BPI-1/88

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877

YOCON®

YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

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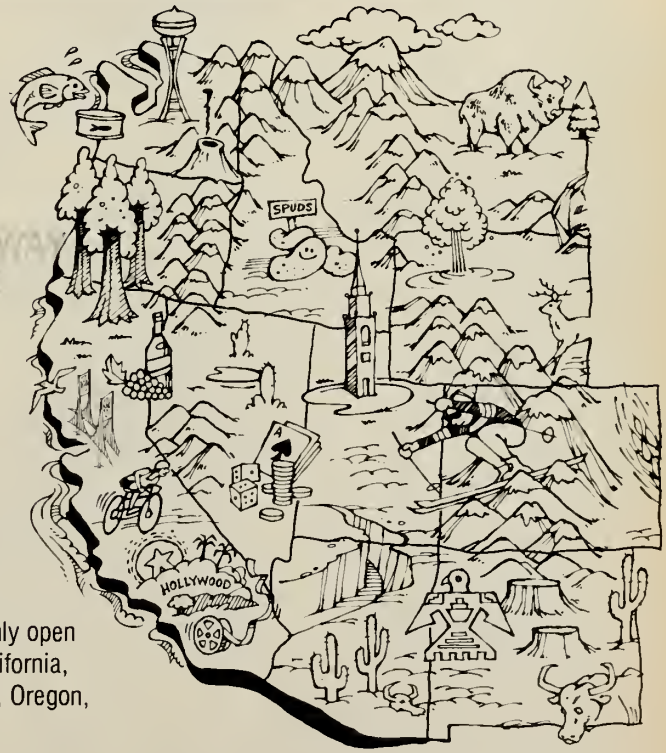

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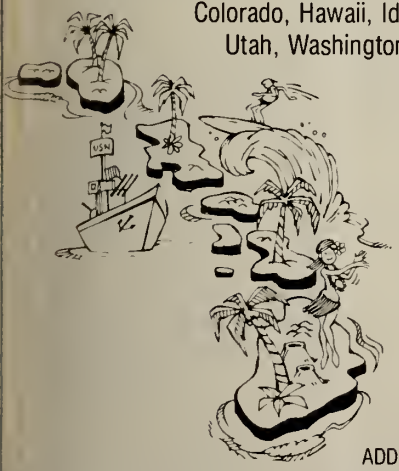

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INDICATIONS AND USAGE. ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk (See WARNINGS.) **CONTRAINDICATIONS.** ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **DRUG INTERACTIONS. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL. **Agents Increasing Serum Potassium:** ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Lithium:** Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. **Human Experience:** There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use the ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressores as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established **ADVERSE REACTIONS.** ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia. (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response.

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In Memoriam

Arizona Medical Association

BONNET, JOE L., Phoenix. Died May 30, 1989, aged 70. Graduate of Duke University School of Medicine, Durham, North Carolina, 1949. Licensed in Arizona in 1951. Dr Bonnet was a member of the Maricopa County Medical Society.

❧

COLTON, WARREN A., JR, Scottsdale. Died Aug 21, 1989, aged 74. Graduate of University of Minnesota Medical School, Minneapolis, 1942. Licensed in Arizona in 1953. Dr Colton was a member of the Maricopa County Medical Society.

❧

GROBE, JAMES L., Phoenix. Died Aug 12, 1989, aged 68. Graduate of Medical College of Virginia School of Medicine, Richmond. Licensed in Arizona in 1953. Dr Grobe was a member of the Maricopa County Medical Society.

❧

WESTERVELT, MARCUS W., Tempe. Died Jul 15, 1989, aged 81. Graduate of University of Cincinnati College of Medicine, 1936. Licensed in Arizona in 1937. Dr Westervelt was a member of the Maricopa County Medical Society.

California Medical Association

BENNETT, ANN, Redwood City. Died Jul 24, 1989, aged 43. Graduate of University of Texas Medical Branch, 1976. Licensed in California in 1979. Dr Bennett was a member of the San Mateo County Medical Society.

❧

BLUM, ETON F. Died Aug 14, 1989, aged 63. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Blum was a member of the Los Angeles County Medical Association.

❧

FREEMAN, EDWARD E., Fullerton. Died Jul 4, 1989, aged 57. Graduate of Albany Medical College, Albany, New York, 1958. Licensed in California in 1964. Dr Freeman was a member of the Orange County Medical Association.

❧

GARDNER, JOHN. Died Jul 15, 1989, aged 85. Graduate of State University of New York Downstate College of Medicine, 1928. Licensed in California in 1951. Dr Gardner was a member of the Los Angeles County Medical Association.

❧

NETHERY, WINSTON G. Died Jun 10, 1989, aged 79. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1934. Licensed in California in 1934. Dr Nethery was a member of the Los Angeles County Medical Association.

❧

PERSYKO, ISAAC, Stockton. Died Jul 26, 1989, aged 82. Graduate of University of Warsaw, 1935. Dr Persyko was a member of the San Joaquin County Medical Society.

❧

PHILO, FRANK G. Died Jul 3, 1989, aged 72. Graduate of University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Dr Philo was a member of the Los Angeles County Medical Association.

ROOT, RALPH N. Died Jul 25, 1989, aged 82. Graduate of University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Dr Root was a member of the Los Angeles County Medical Association.

❧

STRATTE, PAUL B. Died Aug 6, 1989, aged 73. Graduate of Rush Medical School, Chicago, 1941. Licensed in California in 1947. Dr Stratte was a member of the Shasta-Trinity County Medical Society.

❧

TARAIL, ROBERT, Redwood City. Died Aug 11, 1989, aged 70. Graduate of University of Minnesota Medical School, Minneapolis, 1943. Licensed in California in 1963. Dr Tarail was a member of the San Mateo County Medical Society.

❧

WILSON, JOHN S., SR, Burlingame. Died Aug 2, 1989, aged 67. Graduate of University of Kansas School of Medicine, Kansas City, 1945. Licensed in California in 1948. Dr Wilson was a member of the San Mateo County Medical Society.

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Placebo-like side effect profile at the 1 mg dose

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1 mg Tablets

When more than a thiazide diuretic is needed

A·H·ROBINS

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride

Precautions: General. Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases, although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n=	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n=279)	Clonidine (n=278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n=20), weakness (n=12), constipation (n=7), somnolence (n=3), nausea (n=3), orthostatic hypotension (n=2), insomnia (n=1), rash (n=1), nightmares (n=1), headache (n=1), and depression (n=1).

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 19-20—**Far West Image Perception Conference.** Westward Look Resort, Tucson. Thurs-Fri. Contact: U of A, CME, (602) 626-7832.

October 27-28—**Therapeutics Update.** Poco Diablo Resort, Sedona. Fri-Sat. Contact: U of A, CME, (602) 626-7832.

November 3—**Infectious Disease Update.** Arizona Health Sciences Center, Tucson. Fri. Contact: U of A, CME, (602) 626-7832.

November 3-4—**Neuro-oncology and Stereotactics: Current Approaches to CNS Neoplasia.** Hyatt Gainey Ranch Resort, Scottsdale. Fri-Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 4—**Practice for an Aging Population: What Will It Be Like in the 1990s.** Sonora Desert Hospital, Tucson. Sat. Contact: Gail Kershner Riggs, (602) 626-6854.

November 9-11—**Second Annual Spine Workshop.** Camelback Inn, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix 85013.

November 10-11—**9th Annual Southwestern Poison Symposium.** Doubletree Hotel, Tucson. Fri-Sat. Contact: Arizona Poison Control Center, (602) 626-6016.

November 18—**Techniques in Gynecologic Surgery: Slide and Video Conference.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Mon. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 18-19—**Neoplasms and Diseases of the Head and Neck.** Arizona Society of Pathologists, Scottsdale Hilton. Contact: Beverly Reichter, (602) 246-8901.

December 1-2—**External Rhinoplasty Course.** Tucson. Fri-Sat. Contact: Ruth Ann Lynn, (602) 626-7764.

December 2-3—**Arizona Chapter, American College of Surgeons.** Westward Look Resort, Tucson. Sat-Sun. Contact: U of A, CME, (602) 626-7832.

December 13—**Dean's Education Rounds.** Arizona Health Sciences Center, Tucson. Wed. Contact: Jack Roberts, (602) 626-4555.

December 14—**Genetics Update.** Flagstaff Medical Center, Flagstaff. Thurs. Contact: H. Eugene Hoyme, MD, (602) 795-5675 (Tucson) or William Austin, MD, (602) 774-1811 (Flagstaff).

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

February 11-16—**International Congress III: Lasers, Stents, and Interventions in Vascular Disease.** Arizona Heart Institute, Scottsdale. Contact: Erika Scott, (602) 266-2200.

February 23-25—**Anesthesia for the 1990s.** Arizona Society of Anethesiologists, Wyndham Paradise Valley Resort, Scottsdale. Contact: Beverly Reichter, (602) 246-8901.

March 1-4—**A Continuance of Excellence.** Arizona Academy of Family Physicians, The Registry Resort, Scottsdale. Contact: Nancy Reeves, (602) 249-2021.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 19-21—**Western Society of Allergy and Immunology: 28th Annual Meeting.** Western Society of Allergy and Immunology at Hotel del Coronado, San Diego. Thurs-Sat. $120. Contact: Joyce Gullixon, PO Box 1119, Portland, OR 97207. (503) 224-6159.

ANESTHESIOLOGY

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. 12 hrs. $325. Contact: UCD.

January 11-14—**Anesthesia Update 1990.** UCSD at Hotel Del Coronado, Coronado. Thurs-Sun. Contact: UCSD.

January 14-19—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Sat. Contact: Murray G. Atnikov, MD, PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 9-13—**64th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Fri-Tues. Contact: IARS, 3645 Warrensville Center Rd, Cleveland, OH 44122-5280. (216) 295-1124.

CARDIOLOGY

October 13-14—**Coronary Heart Disease Update.** Medical Education Resources at Sheraton Fisherman's Wharf, San Francisco. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

October 27-29—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Bally's Casino Hotel, Las Vegas, Nevada. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

(Continued on Page 384)

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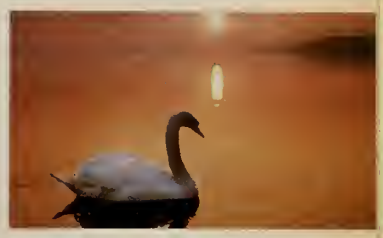

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For Brief Summary, please see following page.

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986;80(3B) 17-21 **2.** Lucki I, *et al*: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987;23 207-211 **3.** Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987;82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride.
Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment.
Precautions: *General*—*Interference with cognitive and motor performance*: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.
Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures
Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).
Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.
Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.
Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur
Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed.
Nursing Mothers—Administration to nursing women should be avoided if clinicaffy possible.
Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age
Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg
Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment
Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement
Associated with Discontinuation of Treatment—The more common events causing discontinuation included. central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1 1%), primarily headache and fatigue. In addition, 3 4% of patients had multiple complaints, none of which could be characterized as primary
Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: Tachycardia/palpitations 1% *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*. Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal*. Musculoskeletal aches/pains 1% *Neurological*. Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin*: Skin rash 1% *Miscellaneous*. Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%
Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare. cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent: dream disturbances; infrequent. depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent. tinnitus, sore throat, nasal congestion; infrequent. redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent. flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare. burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent. muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent. decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent. edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent. weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.
Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.
Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance
Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).
Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.
Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined
For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.
U.S. Patent Nos. 3,717,634 and 4,182,763
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CONTINUING MEDICAL EDUCATION

(Continued from Page 382)

November 3-4—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Rancho Las Palmas, Rancho Mirage. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

December 1-2—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 10-12—**Cardiovascular Disease in the Elderly.** UCI at Fess Parker's Red Lion Resort, Santa Barbara. Wed-Fri. Contact: UCI.

January 19-20—**Coronary Heart Disease Update.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $325. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

DERMATOLOGY

October 14-15—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF at Laurel Heights Campus. Sat-Sun. 10 hrs. $205. Contact: UCSF.

November 2-5—**International Hot Spots in Dermatology: The Patient, the Disease, the Physician and the Art.** Kauai Academy of Continuing Education at Stouffer's Waiohai Beach Resort, Poipu, Hawaii. Thurs-Sun. Contact: David J. Elpern, MD, PO Box 457, Kalaheo, HI 96741.

January 18-20—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande at Torrey Pines, La Jolla. Thurs-Sat. $400. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 386)

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(Continued from Page 384)

January 19-21—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess. Fri-Sun. Contact: UCSD.

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. $415. Contact: UCD.

December 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. $450. Contact: UCSD.

December 7-9—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 16 hrs. $220. Contact: UCSF.

December 11-15—**Emergency Medicine Symposium III.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

January 17-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Maui, Hawaii. Wed-Sun. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 17-20—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Las Vegas, Nevada. Sat-Tues. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 18-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Los Angeles. Sun-Wed. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. Contact: UCSD.

INTERNAL MEDICINE

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 18 hrs. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

October 30-November 3—**Hyperbaric Medicine.** Long Beach Memorial Medical Center. Tues-Sat. 36 hrs. $650. Contact: George Hart, Dept of Baromedicine, 750 E 29th St, Signal Hill 90806. (213) 595-3943.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

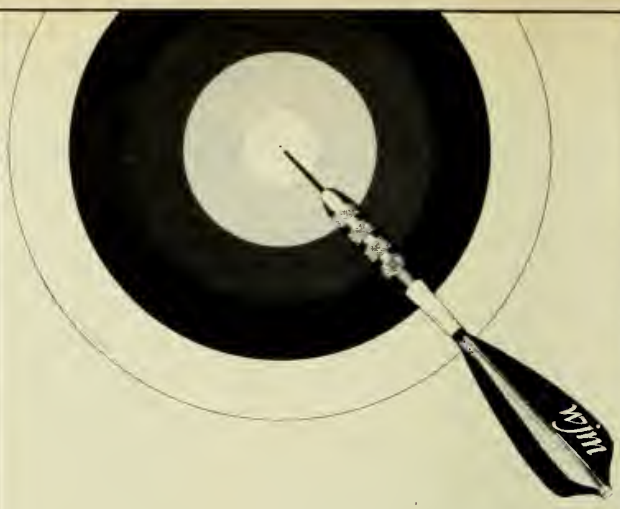
November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. 16 hrs. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 18-21—**Advances in Gastroenterology.** UCSD at Hotel Del Coronado, San Diego. Thurs-Sun. 23 hrs. $425. Contact: UCSD.

January 19-20—**The Medical Dysphagia Team: From Intensive Care to Rehabilitation.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

(Continued on Page 388)



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(Continued from Page 386)

January 25-27—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 2-3—**7th Annual Reider Laser-Urology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 3-4—**Searching for New Horizons in Non-Invasive Technology: The Next Decade.** UCSF at Union Square Holiday Inn, San Francisco. Sat-Sun. $200. Contact: UCSF.

February 9-10—**2nd Annual Bristol Myers Symposium on Neurosciences.** UCSD at Price Center, La Jolla. Fri-Sat. 12 hrs. $50. Contact: UCSD.

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 18-25—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. One week. Contact: UCD.

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5-6—**Advanced TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

OB/GYN

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

January 28-February 1—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 2-3—**7th Annual Reider Laser-Gynecology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

OPHTHALMOLOGY

December 1—**Phacoemulsification and IOL Update.** UCI at Center for Health Education, Long Beach. Fri. Contact: UCI.

December 14-15—**Update: Pediatric Ophthalmology.** UCSF at Hyatt Regency, San Francisco. Thurs-Fri. Contact: UCSF.

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

PEDIATRICS

October 13-14—**Pediatric Advanced Life Support.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 3-5—**Current Advances in Pediatrics.** American Academy of Pediatrics California Chapter 4 at Disneyland Emerald Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: California Chapter 4, AAP, PO Box 1297, Orange 92668. (714) 978-2415.

November 4—**Pediatric Protein Metabolism.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 12-13—**North American Society for Pediatric and Adolescent Gynecology** at Red Lion Hotel, Costa Mesa. Fri-Sat. Contact: UCI.

January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

February 2-4—**Current Concepts in Pediatric Medicine 1990.** Children's Hospital at Hyatt Islandia, San Diego. Fri-Sun. Contact: Children's Hospital and Health Center, Medical Education Dept, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

PSYCHIATRY

October 13-15—**California Psychiatric Association Annual Meeting** at Del Coronado Hotel, San Diego. Fri-Sun. Contact: Barbara Gard, 221 Main St, Ste 352, San Francisco 94105-9832. (415) 882-5196.

October 26-29—**Psychosomatic Medicine and Consultation-Liaison Psychiatry in a High-Technology World.** Academy of Psychosomatic Medicine at Riviera Hotel, Las Vegas, Nevada. Thurs-Sun. Contact: Academy of Psychosomatic Medicine, 5824 N Magnolia, Chicago, IL 60660. (312) 784-2025.

October 1989-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

November 10-12—**35th Annual Group Therapy Symposium: Focus on Leadership.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. 21 hrs. $195. Contact: UCSD.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

RADIOLOGY

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 10-12 and January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

December 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 60009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

(Continued on Page 390)

What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

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We developed ways to speed up claims processing and payments. So you can spend more time worrying about patients, and less time worrying about paperwork.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 388)

February 1-4—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 16 hrs. $375. Contact: UCSD.

March 2-4—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-7—**Neuroradiology Update.** UCSD at Hotel del Coronado, San Diego. Mon-Wed. 18 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Tues-Fri. 23 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-9—**Combined Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**MRI for the Technologist: Symposium and Workshops.** UCSD at Hotel del Cornado, San Diego. Tues-Fri. 21 hrs. $275. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

October 1989-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October-June—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 38 hrs. $1125. Contact: UCSD.

October 27-28—**Artificial Knee Conference.** UCI at Center for Health Education, Long Beach. Sat-Sun. 11 hrs. Contact: UCI.

November 13-15—**21st Annual Surgical Congress.** Orange County Surgical Society at Le Meridien Hotel, Newport Beach. Mon-Wed. 16 hrs. Contact: OCSS, PO Box 1297, Orange 92666. (714) 978-3983.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

January 22-26—**13th Annual Assembly in Surgery.** UCSD at Catamaran Resort Hotel. Mon-Fri. Contact: UCSD.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

OF INTEREST TO ALL PHYSICIANS

October 13-15—**Medical Office Laboratory Second Annual Conference.** San Diego State University at Mission Valley Marriott Hotel. Fri-Sun. 17 hrs. Contact: SDSU, College of Extended Studies, Certificate Program, San Diego, CA 92182. (619) 594-6255.

October 14—**29th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott Hotel. Sat. Contact: Sylvie Tarro, (213) 641-8152.

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 21—**9th Annual Norman Sharrer Symposium: Common Difficult Treatment Syndromes.** Kaweah Delta District Hospital at Holiday Inn, Visalia. Sat. 6 hrs. $25. Contact: Kaweah Hospital, 400 W Mineral King Ave, Visalia 93291. (209) 625-7308.

October 28—**Current Concepts in Medicine 1989.** Los Angeles County Medical Association and Antelope Valley Medical Center at Desert Inn Hotel, Lancaster. Sat. 7 hrs. $60. Contact: Sue Crimin, (805) 949-5942.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 2-4—**The Challenge of Diabetes.** Annenberg Center for Health Sciences at Eisenhower at Rancho Mirage. Thurs-Sat. 15 hrs. Contact: Registration Secretary, (800) 321-3690.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 6-9—**Primary Care Update: 74th Scientific Assembly.** Interstate Postgraduate Medical Association at Town & Country Hotel, San Diego. Mon-Thurs. 24 hrs. $200. Contact: IPMA, PO Box 5474, Madison, WI 53705. (608) 257-1401.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

November 30-December 2—**California Trauma Conference.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas Hilton. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 2—**7th Annual Reider Laser Center International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers With ND: YAG Laser Workshop.** UCI at Center for Health Education, Long Beach. Contact: UCI.

December 6—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda at Los Angeles. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 891-2473.

December 9-10—**Travel Medicine '89.** American Society of Tropical Medicine and Hygiene at Honolulu, Hawaii. Sat-Sun. 12 hrs. $250. Contact: Linda Limauro, 20 York St, New Haven, CT 06504. (203) 785-2476.

December 11-12—**Clinical Care of the AIDS Patient.** UCSF at Hyatt Regency Embarcadero, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 16-20—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 40 hrs. $295. Contact: UCLA.

January 20—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $110. Contact: Kim I. Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

January 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Kona Surf Resort, Kona, Hawaii. 1 week. 21 hrs. $395. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

January 27-28—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Holiday Inn Union Square, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

February 1-3—**13th Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Mon-Fri. Contact: UCSD.

February 7-9—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 21 hrs. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 9-10—**Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 22 hrs. $350. Contact: UCSD.

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IT MAY CHANGE THE WAY YOUR PATIENTS FEEL ON ANTIHYPERTENSIVE THERAPY

FOR MANY HYPERTENSIVE PATIENTS
START WITH ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

For a Brief Summary of Prescribing Information,
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VASOTEC®

(ENALAPRIL MALEATE | MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions.

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome: Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Vasculitis, muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium <130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS18R2(817)

MSD
MERCK SHARP & DOHME

CONTINUING MEDICAL EDUCATION

(Continued from Page 390)

March 2—**16th Annual Diabetes Symposium.** UCD at Hilton Inn, Sacramento. Fri. Contact: UCD.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

March 31-April 7—**Primary Care Medicine.** UCSF at Maui, Hawaii. One week. $475. Contact: UCSF.

IDAHO

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** University of Washington at Sun Valley. Fri-Sun. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 441-9762.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 18—**Affective Disorders.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

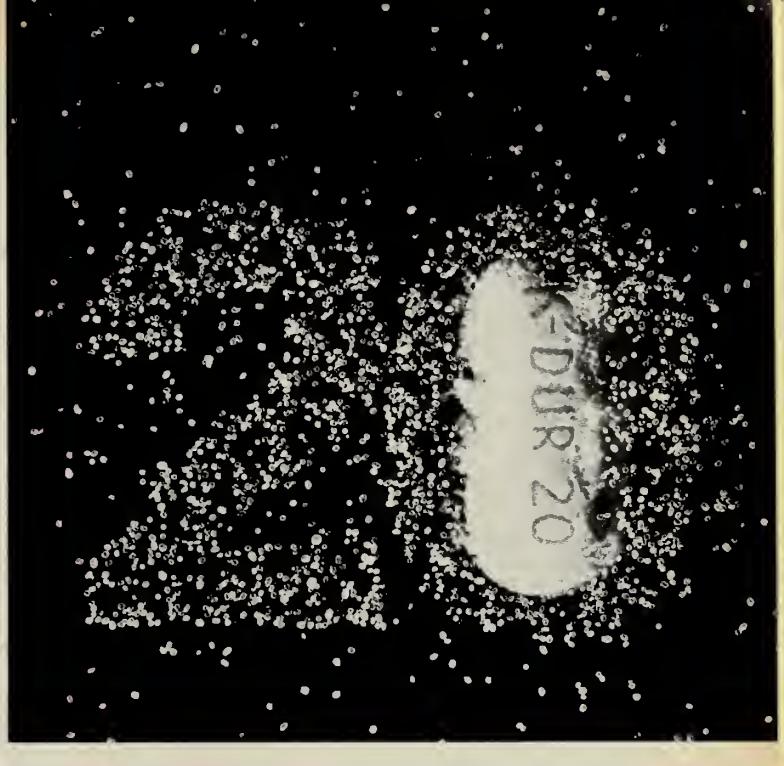
January 20—**Neuropsychiatry.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education,

(Continued on Page 396)



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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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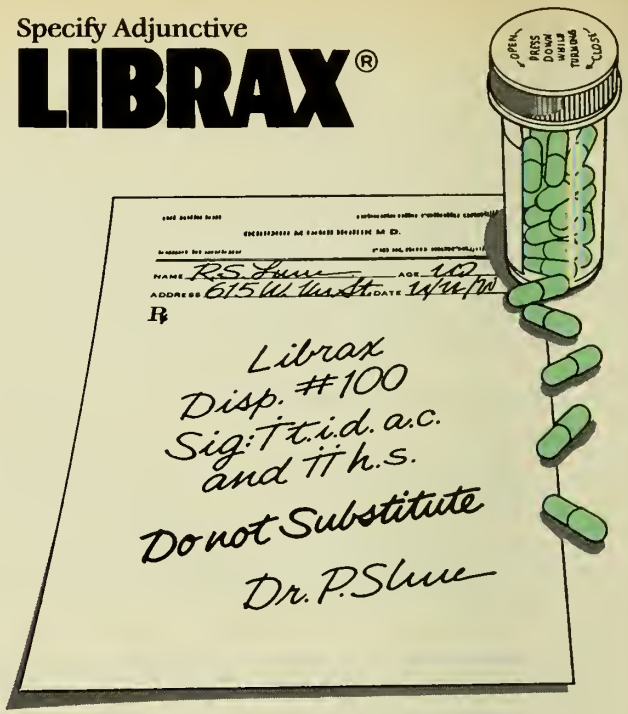

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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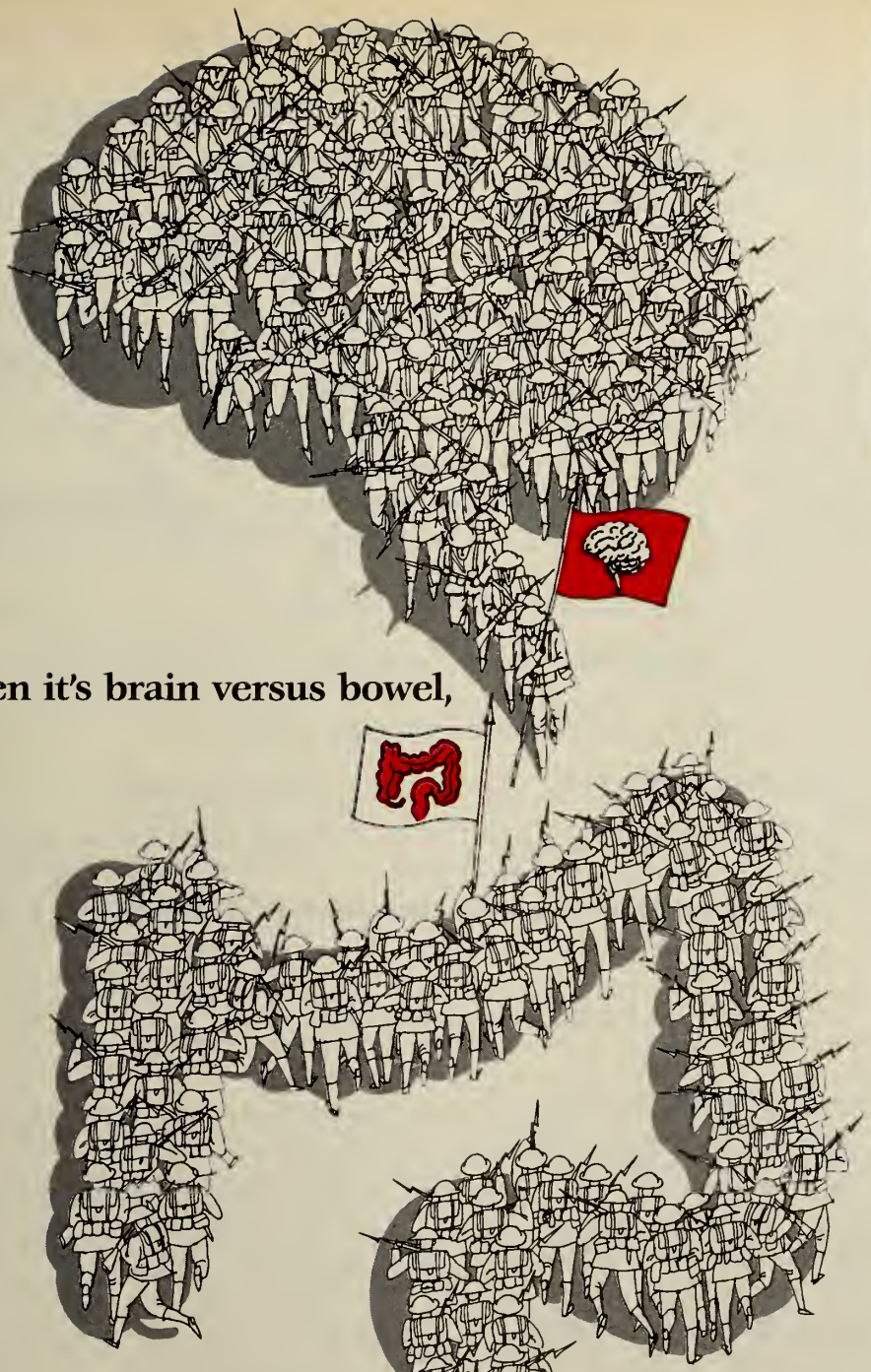

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*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

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Please see summary of prescribing information on adjacent page.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 393)

540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 397)

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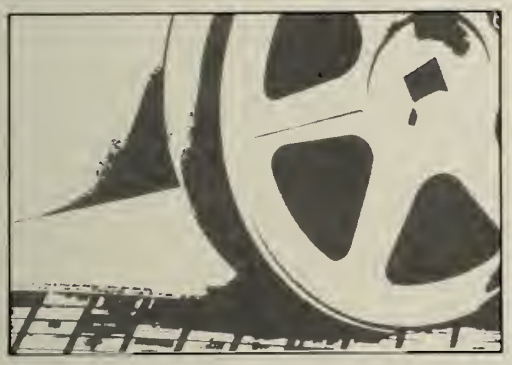

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CONTINUING MEDICAL EDUCATION

(Continued from Page 396)

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 18—**Nutrition.** Seattle. Wed. Contact: NW Hospital, (206) 368-1623.

October 19-20—**Office Management of Pain.** Seattle. Thurs-Fri. Contact: U/W.

October 19-21—**Washington State Academy of Physician Assistants Annual Fall Meeting.** Seattle. Thurs-Sat. Contact: VMMC.

October 26—**Annual Combined Medical Staff Meeting.** Everett. Fri. Contact: Pacific NW Medical Education Institute, (206) 258-6322.

October 27-28—**Sinus Surgery.** Seattle. Fri-Sat. Contact: U/W.

October 27-28—**Acid-Peptic Disease: New Perspectives.** Seattle. Fri-Sat. Contact: VMMC.

November 3—**The Injured Knee: Diagnosis, Treatment, and Therapy.** Seattle. Fri. Contact: VMMC.

November 3-4—**Medical Updates—School of Medicine.** Seattle. Fri-Sat. Contact: U/W.

November 10—**Sexual Abuse in Medical Practice.** Location to be announced. Fri. Contact: U/W.

November 10—**Outpatient Treatment of Infections: Oral Antibiotic Therapy.** Seattle. Fri. Contact: VMMC.

(Continued on Page 401)

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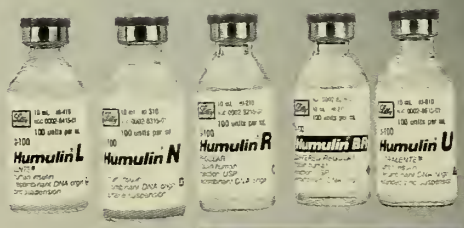

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The Western Journal of Medicine

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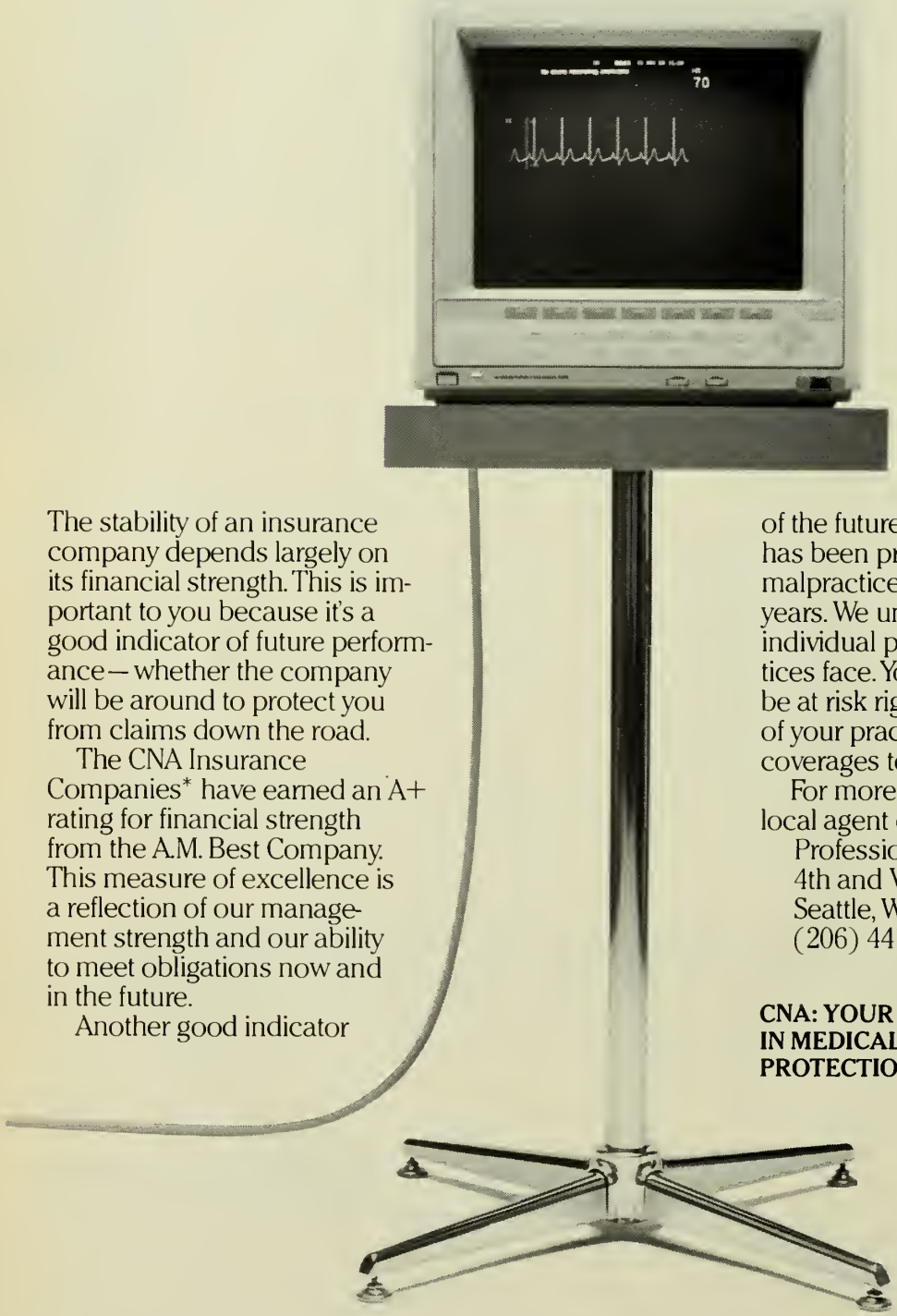

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Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported. Increased serum transaminase has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported. Increased plasma creatinine has been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

October 1989, VOL. XLVI, No. 10

Crunch Time: Are We In or Out? Part II

Marshall B. Block, M.D.

At the moment none of us knows how effective we really are in our day to day activities as practicing physicians. Although we think we are doing the right thing, how can we be sure? How frequently should my patients with diabetes mellitus develop ketoacidosis during a lifetime? Should they develop ketoacidosis at all? How frequently should women have hysterectomies? TURPs? Our statistical data shows that the operation varies in frequency depending upon geographic considerations. Why is this so? Long term, do patients who have hysterectomies and TURPs have less or more medical problems? No one presently knows the answers to these questions. They are only a small number of many uncertainties which exist within medicine today. To answer questions such as these, one needs to assess the long term outcome of patients. This information heretofore has been sacrosanct.

Various reviewers have attempted to see our medical records. HMOs, IPAs and PPOs as well as third party carriers have asked at various times for health records depending upon various needs. I wonder how many of us feel comfortable sending our office records to such reviewers. What form and type are medical records presently in in most of our offices? Do we include appropriate information so that an outside observer will know what we were thinking when we did certain things? When we ordered certain tests? When we considered certain procedures?

Medical records initially started as a personal diary for physicians. They were notes and observations that the physician made to help him remember a patient's medical condition. Since then the use of medical records has undergone a dramatic change. They are really no longer considered the personal property of the physician but rather the patient's history. We are in effect the patient's biographers. As such, they are open to review and need to be formalized in a fashion which can be read and understood. With greater accountability to all payers of health care bills, we must be able to justify what we do. Would any of us allow a construction person to remodel our home without first having him itemize all of the changes and the change orders? Would we not want to know ahead of time what he was going to do and why he was doing it? Similarly, our records must state why something was done before it was done, not retrospectively.

In previous editorials I have emphasized the increasing need for better medical records. The thoughts were not original nor unique but needed to be repeated as the importance of medical record review evolved. The ability to carefully monitor multiple medical problems over a long period of time requires careful and sophisticated documentation. The transition from handwritten random record keeping to a "soap" format (the Weed System) is one that can have positive effects for the physician. Not only will it make his records more amenable to review, it will organize the physician's medical care of the patient. It will make certain that medical problems of a chronic nature are not overlooked or forgotten. It will permit serial evaluation of medical problems. As our population ages, their medical problems increase in number and severity. In order to document all of these things, the problem oriented record will enable the physician to constantly keep abreast of these problems. It will furthermore save the physician time in recording and responding to various requests for medical records by having medical records that are explicitly clear. It will enable outside reviewers to use the medical record as a medical history and will thus not require additional dictation

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In This Issue:

- Hypertension: The Current Challenge
- New Members
- Physicians in the News
- Classified Advertising

From Our President

Mark Ivey, Jr., M.D.

It is a true privilege to be able to communicate with the physicians out there who have wisely invested in the Arizona Medical Association. Who else do you know in Arizona who has dedicated time and money toward preserving our profession?

What organization, bureaucrat, politician or "allied health care provider" spends time, energy, money and conscience in an effort dedicated toward putting the patient first?

A few weeks ago I attended the annual Rural Health Conference and was again forcibly reminded of how many non-physicians have the ability to influence patient care decisions, and how much real power these people have. Although we think we know how completely third party payors and government agencies have invaded our turf, there's a lot more going on out there that we still are not fully aware of, and it's scary.

I guess, like many of you, I'm just sick and tired of these people telling me how to practice medicine, imposing new rules and regulations, cutting care in the name of cost containment, and not listening when I say I can't pay any more for malpractice coverage.

Organized medicine is the last bastion from which we can continue the fight for our right to make the decisions which will give our patients the best possible care. And we are making progress, both nationally and on the state level.

In Arizona, all of us are happy that the periodic payment bill passed and that a small amount of money has been set aside to subsidize costs for rural obstetrics. But most of us are certain that these bandaids will not stop the hemorrhage of dollars into legal coffers or prevent physicians from moving out of the practice of medicine and surgery.

Effectiveness in fighting for our cause depends on how many of us have joined together or are willing to get involved. It has been proven time and again that a group which represents 90 percent of its potential members has far more clout than another which only represents half those eligible. And today clout is the name of the game, to make our legislators, government administrators and other key decision makers listen to our concerns and respond to our needs.

I can't really understand why almost half of the physicians in the state haven't joined ArMA. I'm convinced that third-party payors, hospitals, governments, both state and federal, and lawyers are not primarily concerned with your medical practice.

ArMA fought hard for the new Industrial Commission reimbursement increase, the periodic payment bill, judicial reform and tracked well over 100 legislative bills affecting medicine. We have also developed a for-profit subsidiary to help physicians manage what monies they can save from the rest of the world with their hands in our pockets.

It is encouraging that we have had over 250 physicians join us just in the last few months; but many of your friends need to be asked: Why haven't you joined? Why do you continue to enjoy the benefits of ArMA's hard work without accepting your share of the responsibility?

Finally, let us serve notice once and for all that the practice of medicine is first and foremost for our patients, regardless of who pays the bill. I hope this note to my friends and fellow physicians is received well, but as your President, I feel obliged to tell it as it is. ■

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Hypertension: The Current Challenge

Hypertension has been well recognized to be a major contributor to strokes, myocardial infarction, congestive heart failure and renal failure. Currently, 58 million Americans are hypertensive if cutoff values of 140 mmHg systolic or 90 mmHg diastolic are used as diagnostic criteria. Fifty percent of Americans over the age of 60 are hypertensive by these criteria. The cost of medication to treat hypertension in the United States was over 2 billion dollars in 1985 and is anticipated to exceed 4 billion dollars by the year 2000. The total economic costs of hypertension are many times that amount. Aggressive programs to identify and treat patients with hypertension have been fairly successful, and have received much of the credit for the 50% reduction in stroke incidence since 1972.

Many challenges of the past have been met. The role of hypertension in coronary artery disease, stroke, heart failure and kidney failure has been identified. The benefits of treatment of hypertension in the prevention of stroke, heart failure and kidney failure have been demonstrated. More effective and better tolerated drugs have been developed. We now have available for treatment of hypertension at least two drugs in each of the following groups: diuretics, beta blockers, centrally acting agents, selective alpha blockers, nonspecific vasodilators, angiotensin converting enzyme inhibitors and calcium entry blockers. Ten or more distinct chemical entities will be available in at least four of these groups by the turn of the century.

Many challenges remain, and perhaps the greatest of these is to avoid a loss of interest in hypertension. With many of the major questions answered and problems solved, and with no fundamentally different antihypertensive drugs likely to appear before the turn of the century, it is tempting to turn research and clinical attention elsewhere. Although the value of therapy is established, and many excellent agents are available, important challenges remain.

It has been difficult to demonstrate a benefit of antihypertensive treatment on coronary artery disease. Whether these are methodologic problems or due to potentially atherogenic or proarrhythmic effects of agents employed in earlier studies is unclear. However, this question of potentially atherogenic and/or proarrhythmic effects on cardiovascular deaths is critical to the choice of antihypertensive therapy.

Some antihypertensive agents can decrease left ventricular mass in patients with left ventricular hypertrophy due to hypertension, while other agents do not cause regression. Whether or not a decrease in left ventricular mass results in an improvement in left ventricular function or a decrease in cardiovascular morbidity or mortality remains to be demonstrated. Only when one of these end points can be proven, will we be justified in basing antihypertensive therapy on the ability of the agent to decrease left ventricular mass.

A final challenge is to evaluate drugs and use them optimally. Only well designed and conducted clinical trials can establish which drugs within a class have significant benefits, and under what circumstances. Only further research can establish what, if any, clinical guidelines are of use in choosing agents for use. Only better education in basic and clinical pharmacology can lead to more rational use of antihypertensive drugs as single agents and in combination, in order to maximize efficacy and minimize adverse effects.

The challenges remaining in hypertension are less grand than the challenges of the past, but they are no less difficult or important. ■

Timothy C. Fagan, M.D.
Associate Professor of Medicine
College of Medicine
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1988 Taxable Equivalent Yield Table for Arizona

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Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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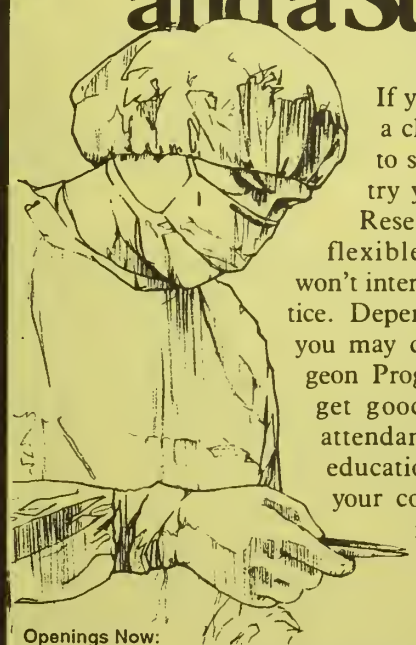

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Physicians in the News

Soviet medical technology was used in Phoenix to repair the leg of a 15-year-old Afghani refugee whose limb was shattered by Soviet war machinery five years ago.

An orthopedic surgeon at Children's Health Center of St. Joseph's in Phoenix used a procedure developed by a Russian surgeon to repair the damaged right leg of young Najebullah Barak.

Najebullah, a refugee from Afghanistan, was injured in Russian rocket fire that left him with a crooked right leg several inches shorter than the left limb. On June 14, **Vincent Russo, M.D.**, performed a three-hour bone-lengthening surgery that was developed in 1951 by Rssian physician Gavriel Ilizarov, M.D. It is arely done in the U.S.

The surgery involved carefully sawing through the right femur, or lower leg, without destroying the blood supply in the medullary canal, the center of the bone. Long thin metal pins were then inserted horizontally at either end of the severed bone through the skin, muscle and bone. The pins are attached externally to a steel frame consisting of metal hoops that encircle the leg above and below the cut bone. The hoops are separated by metal rods and are connected to a complex arrangement of tension wires that were tightened with bolts four times a day to pull the severed femur apart, allowing new bone to grow and fill in the gap.

Najeeb's right leg was not only short but also severely angulated, and the knee joint, which was blasted by rocket fire, was fused. By straightening and lengthening the bone, Russo hopes to achieve 7 cm (approximately 3 inches) of growth. In Europe, where bone lengthening surgery has been done for years, doctors are achieving eight inches or more of growth. The procedure has been used there, and more recently in the U.S., to bring persons with short-stature dwarfism to near-normal height.

Russo has waived his fee for the surgery, and hospitalization for Najeeb is covered by the Arizona Children's Rehabilitative Services program. The federally funded Refugee Medical Assistance Program provided $9,000 for the external bone-lengthening equipment, called the "Monticelli-Spinelli" device after the two Italian physicians who refined the Russian technology. Dr. Russo is a designated clinical investigator for the device.

Last year, Dr. Russo also reconstructed Najeeb's elbow with a procedure called fascial arthroplasty in which an elbow joint was fabricated from skin and muscle (the fascia) taken from deep in the boy's left thigh. This, too, is a rarely performed surgery in the U.S.

Russo has treated Afghan freedom fighters in the past, only to have them return to their homeland and the war being fought there. Najeeb has been in the U.S. for a year with his mother, younger brother and sister, and his father, who worked for an American construction company in Afghanistan. Najeeb now plans to become a U.S. citizen. The family's move to the U.S. was sponsored by the Tolstoy Foundation. Najeeb was discharged from Children's Health Center of St. Joseph's at the end of July. The bone-lengthening device will remain attached to his leg for three months after he goes home. Since the surgery, he has been walking short distances every day. Early ambulation is crucial to his recovery and the healing of his leg.

According to Dr. Russo, Afghanis injured during the Soviet invasion had to travel over a high mountain range on foot or pack animal for several days in order to reach the most rudimentary medical care in Pakistan. Najeeb's leg and arm were both torn apart in battle and he received only minimal care for his injuries. ■

Crunch Time

Continued from page 1

of a patient's medical history when insurance requests arise. In essence, the time taken to record accurate medical records will save untold time later. With the institution of outpatient review by Medicare, all of us will be faced with office record review. I suspect that if the problem oriented record is not present or if medical records are not legible or if medical records are not complete, the Federal Government and perhaps other third party payers will categorically state that they will not pay for our services. With this in mind, I urge each of you to consider changing again, to a problem oriented record which is legible, preferably typed, so that ultimately when computerization of all medical records takes place the transition will be much easier.

With involvement by physicians in assessing effective medical care, hopefully we will know what we are doing and whether it is appropriate for our patients. At the moment we are still in the dark regarding a great many of our activities. I think the time has come for us to look beyond our paranoia and take the first step, albeit a tenuous one, to help those who want to find the answers to many of the uncertainties in medicine. In so doing this will be our best defense against those who state that physicians have parochial interests and are really no longer a profession. We must show what I believe we all feel, down deep, that there is more to medicine than business--there is a science. We must help found that discipline. ■

Marshall B. Block, M.D.,
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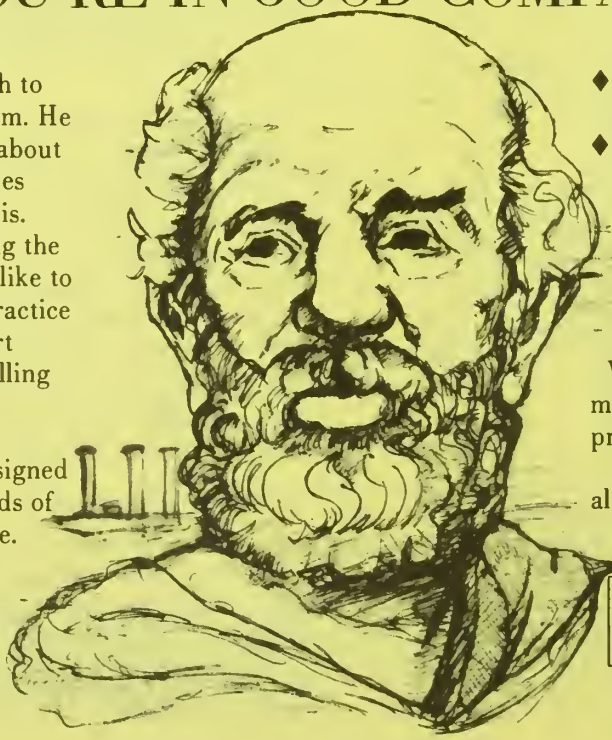

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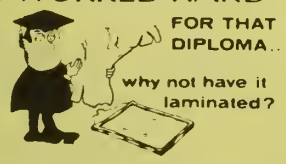

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Clinical Investigation

Antigenic Conservation and Variation in *Giardia* Cysts From Various Vertebrate Hosts

EDWARD T. RILEY, MD, *Portland, and* HENRY H. STIBBS, PhD, *New Orleans*

Monoclonal antibodies produced against Giardia muris *cysts reacted in indirect immunofluorescence with homologous cysts and cysts from a* Giardia-*infected wild Norway rat but did not cross-react with* Giardia lamblia *cysts of human, dog, or beaver sources. Another monoclonal antibody raised against* Giardia simoni *cysts from the Norway rat reacted with homologous cysts (rat) and cross-reacted with cysts from a cow. The demonstration of antigenic differences at the cyst surfaces of* Giardia *organisms of animal and human origin suggests that it is possible to identify the animal source of* Giardia *cysts according to their pattern of reactivity with monoclonal antibodies. Such identification would have a useful application in affirming the possible zoonotic transmission of animal source* Giardia *species to humans.*

(Riley ET, Stibbs HH: Antigenic conservation and variation in *Giardia* cysts from various vertebrate hosts. West J Med 1989 Oct; 151:403-405)

Zoonotic transmission of *Giardia lamblia* cysts to humans through drinking water has been implicated as an important cause of epidemic giardiasis, an important diarrheal disease.[1,2] Identifying the source of the giardial cysts is one of the major challenges facing epidemiologists studying these outbreaks. Many different animals are hosts to *Giardia* species, and transmission experiments have revealed evidence for both cross-host-species transmission and some degree of host specificity for different species or organisms of *Giardia*.[3-6] To compound the epidemiologists' dilemma, different species of *Giardia* are to a large degree morphologically indistinguishable.[7] Consequently, determining the host reservoir—that is, cyst source—in waterborne giardiasis outbreaks and tracing cysts found while monitoring water supplies have been based on speculation and circumstantial evidence.

Clearly, to determine relatedness, a biochemical, antigenic, or genetic method of differentiating giardial cysts is needed for comparing cysts from animal sources, from drinking water, and from persons infected in outbreaks. In answer to this need, we now report the development of monoclonal antibodies that distinguish *G lamblia* (human source) from *Giardia muris* (hamster source) cysts by indirect immunofluorescence.

Materials and Methods

Giardia muris cysts were purified from the feces of experimentally infected nu nu (thymusless) mice, and *Giardia simoni* cysts were isolated from the feces of a naturally infected wild Norway rat. The original source of the *G muris* cysts was an infected golden hamster at Case Western Reserve University (Cleveland, Ohio).[8] The infected rat was trapped along a slough on the University of Washington campus that drains into Lake Washington. Cysts were purified by centrifuging crushed fecal pellets over a solution of 1 mol per liter sucrose in water (ten minutes at 500*g*) followed by centrifuging over two layers of Percoll (Sigma Chemical Company, St Louis, Missouri) of specific gravities 1.05 and 1.09 (ten minutes at 500*g*).[9] Monoclonal antibodies were prepared by immunizing BALB/c mice with the whole, live, freshly isolated, and purified *G muris* cysts through a series of four intraperitoneal injections of about 2×10^6 cysts per animal per injection over six weeks followed by one or two intravenous tail injections, four days apart, of 2×10^6 cysts in a sterile saline solution. Four or five days after the last intravenous injection, the mice were killed and the spleen cell:myeloma cell fusion was carried out. Spleen cells from the immunized mice were fused with NS-1 (P3-NS-1/1-Ag 4.1) mouse myeloma cells grown in RPMI 1640 medium (Gibco) with 15% fetal bovine serum, using 40% polyethylene glycol 1500 by established procedures.[10] Cells were plated onto 96-well culture plates, and hybridomas were selected using RPMI 1640 medium (15% fetal bovine serum) supplemented with HAT—hypoxanthine, 1×10^{-4} mol per liter; aminopterine, 4×10^{-7} mol per liter; thymidine, 1.6×10^{-5} mol per liter. Growth was enhanced by using BALB/c mouse thymus cells as feeder cells.

Hybridomas secreting antibody to the cysts were detected both by indirect immunofluorescence using the homologous cysts dried onto the bottoms of flat-bottomed, 96-well, en-

From the Department of Medicine, Emanuel Hospital, Portland (Dr Riley), and the Department of Pathobiology, University of Washington School of Public Health and Community Medicine, Seattle (Dr Stibbs). Dr Stibbs is currently with the United States-Japan Biomedical Research Laboratories, Tulane University Hebert Center, Belle Chasse, Louisiana.

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ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
PBS = phosphate-buffered saline

zyme-linked immunosorbent assay (ELISA) plates (Falcon ProBind, #3915, Becton Dickinson)—5,000 to 10,000 cysts per well—and by ELISA using 25,000 cysts per well. Stable hybridomas were cloned by limiting dilution three times. Ascitic fluid was produced in BALB/c mice pretreated with 0.3 to 0.5 ml Pristane per mouse (Sigma Chemical Company). Either culture supernatant or ascitic fluid was used in the immunofluorescence cross-testing with cysts from the various animal sources.

For the immunofluorescence cross-testing, cysts were spotted and air-dried onto eight-spot Teflon-coated slides (Bellco, Vineland, NJ) and fixed for five minutes in acetone. Cysts were then exposed to serial dilutions—ranging from 1:10 to 1:200—of monoclonal antibodies in 0.0175 mol per liter phosphate-buffered saline (PBS), pH 7.4, for 60 minutes at 37°C in a humid chamber. Afterwards the cysts were rinsed twice with PBS, then exposed to affinity-purified, fluorescein-conjugated, goat anti-mouse immunoglobulin antibody (Cappel Laboratories, West Chester, Pennsylvania) diluted 1:80 in PBS, and finally the cysts were rinsed again twice in PBS, air-dried, and mounted with PBS:glycerol (1:9) containing 0.1 mg per ml *p*-phenylenediamine to retard fading. The slides were examined under a Zeiss fluorescence microscope at 400 × magnification. An anti-*G lamblia* cyst polyclonal rabbit antiserum was used as a positive control, and preimmune ascites or NS-1 myeloma cell culture supernatant served as negative controls.

Results and Discussion

A total of four monoclonal antibodies were produced against *G muris* cysts and one against the *G simoni* cysts. When *G muris* cysts were reacted with the four monoclonal antibodies raised against *G muris* cysts, they showed a strong reaction at the location of the cyst wall (Figure 1). Cysts from the rat infected with *G simoni* also bound the anti-*G muris* monoclonal antibodies equally strongly (not shown). *Giardia lamblia* cysts from eight human patients, however, did not bind the anti-*G muris* monoclonal antibodies, nor did *Giardia* species cysts from dogs (n = 4), beavers (n = 2), muskrats (n = 3), voles (n = 3), or cattle (n = 1) react with these anti-*G muris* antibodies (Table 1). There was no difference between the four anti-*G muris* antibodies in terms of which organisms they did or did not react with.[10]

In further work with an anti-*G lamblia* monoclonal antibody developed by Riggs,[11] and with the single monoclonal antibody produced against cysts from the rat, *Giardia* species could be grouped according to their patterns of reactivity when cross-tested with the various antibodies (Table 1). The monoclonal antibodies could not differentiate human-, beaver-, or dog-source *Giardia*. Beaver-source *Giardia* has been strongly implicated in many waterborne outbreaks,[12,13] and the experimental transmission of human-source *Giardia* to dogs has been successful.[3,14] Our results suggest that using the pattern of cross-reactivity with the monoclonal antibodies predicts the ability of a *Giardia* strain to infect certain hosts.

Passing the cysts through another host species did not affect the pattern of reactivity. Human-source *Giardia* cysts passed through gerbils or rats, beaver-source cysts passed through gerbils, and *G muris* and *G simoni* cysts passed through gerbils retained their original patterns of reactivity.

One of the most notable findings of the cross-testing experiments was that the pattern of reactivity of the cyst specimens from an individual host species remained constant despite wide geographic differences in the organism's original source—that is, human cyst organisms were from Seattle and Colorado; beaver cyst organisms were from Washington, Vermont, and Alberta. Further evidence for host specificity of cyst antigens is that the wild Norway rat and one of the infected muskrats were trapped in the exact same location on our university campus within two weeks of each other, yet their giardial cysts showed completely different patterns of reactivity (Table 1).

These results are somewhat contrary to those of others who have found intrahost variation to sometimes be as great as interhost variation when trophozoite antigens, restriction endonuclease DNA fragments, and isozyme patterns were examined. These studies showed differences between *Giardia* organisms from the same host species.[15-18] Based on our findings, however, it would appear that in the cysts de-

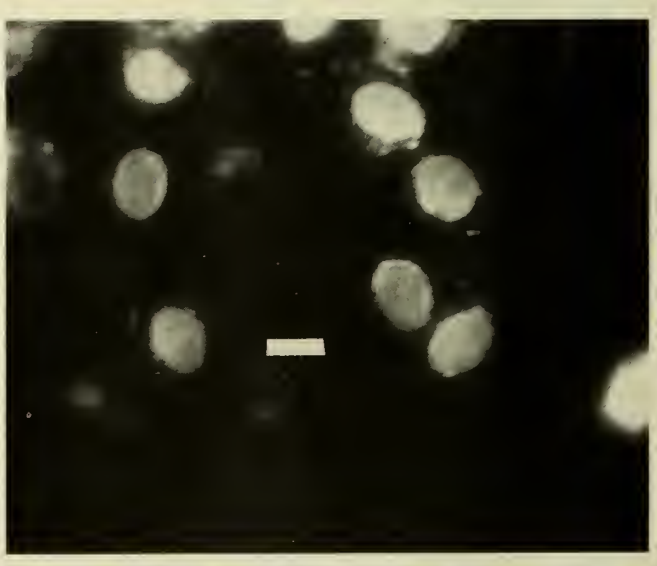

Figure 1.—*Giardia muris* cysts are shown under fluorescent microscopy after exposure to an anti-*G muris* monoclonal antibody followed by a reaction with fluorescein-conjugated goat anti-mouse immunoglobulin antibody (white bar equals 10 microns).

TABLE 1.—*Reactivity of* Giardia *Species Cysts From Various Animal Hosts With Monoclonal Antibodies Raised Against* Giardia muris *(Hamster Source),* Giardia lamblia *(Human Source), and* Giardia simoni *(Wild Norway Rat Source)*

Original Source of Giardia *Cysts*	*Antibodies*		
	Anti-G muris	*Anti-G* lamblia	*Anti-G* simoni
Rat, n=1	++	++	++
Beaver, n=2	–	++	–
Dog, n=4	–	++	ND
Human, n=8	–	++	–
Hamster, n=1*	++	–	–
Cow, n=1	–	–	++
Muskrat, n=3	–	–	–
Vole, n=3	–	–	–

++ = positive reaction, – = negative reaction, ND = No data available

*Source of cysts against which anti-*G muris* antibodies were produced

rived from one host species, certain cyst-wall epitopes are conserved; monoclonal antibodies produced against them can differentiate between the giardial cysts originating naturally from different hosts but do not pick up intrahost *Giardia*-cyst variations. This suggests that the pattern of reactivity of cysts with monoclonal antibodies in immunofluorescence might be a useful criterion for establishing species of *Giardia*. The belief of Filice[19] that, based on morphologic criteria, *Giardia* should be grouped into no more than three species has become widely accepted, at least in North America. Our discovery that some degree of antigenic constancy exists among certain cyst antigens of organisms from individual host species suggests that monoclonal serotyping of cysts provides a supplementary taxonomic criterion that can be superimposed over the basic morphologic divisions Filice established. A great deal more work, however, must be done using a larger number of monoclonal antibodies produced against organisms of *Giardia* from other host species to see if this proposed immunotyping scheme will continue to show antigenic constancy of cyst epitopes within organisms. An expanded system of monoclonal typing may eventually make feasible the identification of the source of cysts found in environmental samples for water-quality monitoring. Monoclonal typing could also prove useful in studying the epidemiology of waterborne giardiasis outbreaks and could provide data regarding which animals may be sources of *Giardia* cysts during outbreaks.

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Trends in *Campylobacter pylori* in Pediatric and Adult Antral Biopsies

A 5-Year Retrospective Analysis

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Campylobacter pylori *has been associated with chronic gastritis and antral ulceration in adults and has recently been reported in children with primary antral gastritis and duodenal ulceration. We reviewed all gastric antral biopsy specimens from children (n = 30) and adults (n = 77) over the past 5 years at the University of California, San Francisco. Tissue sections were stained with Giemsa to detect* C pylori, *and medical histories were obtained by chart review. The prevalence of* C pylori *in antral biopsy specimens with gastritis increased from 22% during the period 1983 to 1986 to 66% in 1987 (P<.001). In all specimens showing gastritis,* C pylori *appeared more frequently in adults (31/67 [46%]) than in children (4/17 [24%]). In cases with primary gastritis, however, the prevalence of* C pylori *reversed to 57% (4/7) in children versus 49% (31/63) in adults. Most children (10/13) with gastritis and no* C pylori *had predisposing conditions. Infection with this organism was associated with more active inflammatory changes in adults than in children, but it may contribute to most cases of hitherto-unexplained gastritis in children. Further studies are needed to determine whether the prevalence of* C pylori *is increasing.*

(Veereman-Wauters G, Ferrell L, Heyman MB: Trends in *Campylobacter pylori* in pediatric and adult antral biopsies—A 5-year retrospective analysis. West J Med 1989 Oct; 151:406-409)

In 1983 Warren and Marshall identified *Campylobacter pylori* in the antrum of adults with active chronic gastritis.[1,2] In several subsequent reports a 50% to 70% incidence of *C pylori* has been described in antral biopsy specimens in adults with nonulcer dyspepsia[3-6] and a 70% to 98% incidence in those of ulcer patients.[3,6] The organism has been reported to fulfill Koch's postulates as a cause for gastritis,[7,8] but its role in peptic ulcer disease remains controversial.[9,10] The data on *C pylori* infection in the pediatric age group are scarce. The organism has been identified on gastric biopsy specimens[11] and successfully cultured from the stomachs of teenagers.[12,13] A retrospective[14] and a prospective[15] study of Canadian children documented a clear association of *C pylori* with primary unexplained gastritis. Epidemiologic studies reveal an increased prevalence of *C pylori* infection with age.[16] Infection with this organism may be dependent on environmental factors; 90% of Peruvians older than 5 years appear to be infected,[9] compared with less than 5% of Americans 22 to 44 years old.[16]

We reviewed all specimens of gastric antral biopsies taken from 1983 through 1987 to determine the prevalence of *C pylori* and associated clinical and histologic features in patients evaluated at the University of California, San Francisco, Medical Center (UCSF).

Patients and Methods

All gastric antral biopsy specimens submitted to the Department of Pathology at UCSF between January 1, 1983, and December 31, 1987, were identified by a computer search. All were taken during an upper gastrointestinal endoscopy carried out by a pediatric or adult gastroenterologist. Biopsy specimens were fixed in 10% neutral-buffered formalin, dehydrated through a series of alcohol and xylene solutions, embedded in paraffin, cut at 5 μm, and stained with hematoxylin and eosin (H & E) (Figure 1). This standard procedure remained unchanged over the study period. *C pylori* was usually readily identifiable on an H & E stain (Figure 2). All pediatric biopsy specimens were stained with Giemsa, but a Giemsa stain was done only in adult biopsy specimens in which *C pylori* was not seen on H & E stain.[17]

The slides of the gastric antral specimens were reviewed by one of us (L.F.), who was blind as to patients' ages and existing diagnoses. Gastritis on the H & E-stained specimens was graded as acute, mild chronic, chronic, or active chronic (acute and chronic), based on the criteria described by Whitehead and co-workers.[18,19] Mucosal invasion of polymorphonuclear cells reflects acute inflammatory epithelial destruction, whereas an infiltrate of the chronic type indi-

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ABBREVIATIONS USED IN TEXT

H & E = hematoxylin and eosin
UCSF = University of California, San Francisco

cates chronic activity that can present in various degrees of severity.

All patient records were reviewed for the indications for endoscopy (Table 1) and the clinical diagnoses. When serial biopsies were done, only the earliest was entered into the study. The presence of gastric or duodenal ulceration was determined endoscopically.

Data were statistically analyzed using the χ^2 test for groups of more than 50 patients and Fisher's exact test for smaller numbers. Differences were considered significant for a P of less than .05.

Results

Temporal Observations

A computer search revealed 107 patients with antral biopsy specimens submitted to the Department of Pathology at UCSF during the five-year period, 1983 through 1987. These specimens were from 30 pediatric patients (younger than 20 years; mean age, 7.4 ± 5.8) and 77 adults (mean age, 54.2 ± 16.6). In all, 84 specimens showed histologic evidence of gastritis; *C pylori* was identified in 35 (42%). In the period 1983 through 1986, the specimens had not been evaluated for the presence of *C pylori*. In 1987, however, 25 biopsy specimens showed *C pylori* by H & E or Giemsa stain, and 22 were correctly diagnosed before our retrospective review. The number of patients with gastric biopsies increased over the study period: specimens were submitted from 55 patients over the first four years (13.8 per year) compared with 52 in 1987 (Table 2). *C pylori* was identified in 25 (66%) of the 38 cases with histologic gastritis from 1987, in striking contrast to the 10 (22%) of the 46 from 1983 through 1986 ($P < .001$, χ^2).

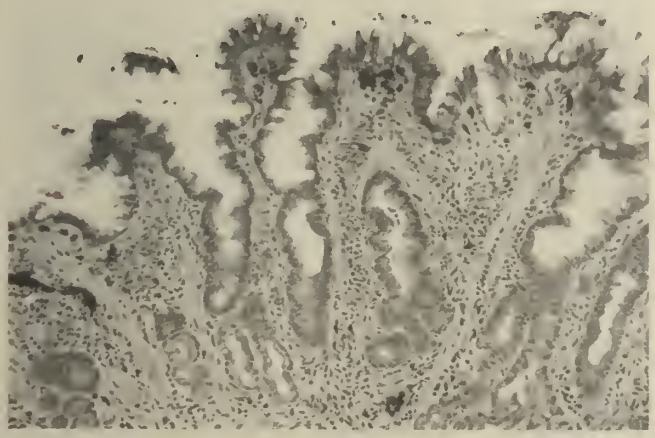

Figure 1.—A gastric antral biopsy specimen shows active gastritis typical of that in adults with *Campylobacter pylori*. The surface and superficial crypt epithelium are mildly hyperplastic (hematoxylin and eosin, × 125).

Figure 2.—A gastric antral biopsy specimen shows *Campylobacter pylori* on the surface of gastric epithelial cells. The bacteria are the curved rods attached to mucin cell luminal surfaces. Bacteria were also observed in the surface mucus (hematoxylin and eosin, × 1,250 oil).

Trends Among Children

In 24 children, indications for endoscopy were epigastric pain or vomiting; in 6 children an endoscopy was done to obtain a biopsy specimen of small bowel to rule out celiac disease. Of the 30 antral biopsy specimens, 17 (57%) showed histologic features of gastritis. *C pylori* was identified in four specimens, one from 1985 and three from 1987. All four showed similar chronic inflammatory changes and were from children evaluated for epigastric pain. Of the remaining 13 cases with gastritis but no *C pylori*, 10 had acute or mild chronic inflammatory changes and 3 only chronic inflammatory changes of the gastric antrum. Of these 13 cases, 10 had predisposing conditions that are generally accepted as a cause of gastritis[14,15,20]: eosinophilic gastroenteritis in 5, using nonsteroidal anti-inflammatory agents in 2, bile reflux viewed endoscopically in 2, and protein-losing enteropathy in 1 patient. *C pylori* infection in children was associated with chronic rather than acute gastritis ($P < .02$, Fisher's exact test). *C pylori* was identified in four of the seven chil-

TABLE 1.—*Indications for Upper Gastrointestinal Endoscopy in Patients With Antral Biopsies Done, 1983 Through 1987*

Indication	Children, n=30, No.	(%)	Adults, n=74,* No.	(%)
Epigastric pain or vomiting	24	(80)	51	(69)
Failure to thrive	6	(20)	..	..
Hematemesis	..		10	(14)
Melena	..		4	(5)
Anemia	..		2	(3)
Anorexia	..		2	(3)
Gastric ulcer, treated	..		1	(1)
Atrophic gastritis, treated	..		1	(1)
Crohn's disease	..		1	(1)
Esophageal varices	..		2	(3)

*Three patients' records were not available for review

TABLE 2.—Campylobacter pylori *in Antral Biopsy Specimens of Children and Adults, According to Study Period*

Study Period and Biopsy Finding	Children, n	CP+	(%)	Adults, n	CP+	(%)	Total, n	CP+	(%)
1983-1986									
Gastritis	9	1	(11)	37	9	(24)	46	10	(22)*
Normal	3	0		6	0		9	0	
1987									
Gastritis	8	3	(38)	30	22	(73)	38	25	(66)*
Normal	10	0		4	0		14	0	
Total	30	4	(13)	77	31	(40)	107	35	(33)

CP+ = biopsy specimen showed *Campylobacter pylori*, n = total number of biopsies done

*$P < .001$ by χ^2 test for 1983-1986 versus 1987.

dren with primary (no underlying factors) gastritis but was not found in the ten with secondary gastritis. None of the children had an ulcer.

Observations Among Adults

Indications for endoscopy in the adult group are listed in Table 1. Of the 77 biopsies, 67 specimens (87%) revealed gastritis. *C pylori* was identified in 31 (46%). The organisms were clearly visible on 18 slides stained with H & E (Figure 2). A Giemsa stain, done on biopsy specimens with gastritis and mucus overlying epithelial cells, led to the identification of *C pylori* in 13 additional cases.

All adults with biopsy-proven *C pylori* infection presented with acute upper gastrointestinal symptoms: epigastric pain and dyspepsia in 29 patients and hematemesis in 2 patients. Of the other 14 patients with suspected upper gastrointestinal tract bleeding (Table 1), 10 had *C pylori*-negative gastritis and 4 had normal findings on the antral biopsies.

Histologic evaluation of the antral mucosa infected with *C pylori* showed acute and chronic inflammatory changes in 23, chronic inflammatory changes in 7, and mild chronic inflammatory changes in 1 patient. Mucosal involvement was less severe in patients without *C pylori:* mild chronic inflammatory changes in 18, acute and chronic inflammatory changes in 9, and chronic inflammatory changes in 9 patients. The association of the organism with acute and chronic or chronic inflammation compared with *C pylori*-negative specimens was significant by χ^2 analysis ($P<.0002$). An underlying cause for gastritis was present in only four adults: Crohn's disease in two, the use of nonsteroidal anti-inflammatory agents in one, and atrophic gastritis in one. *C pylori* was evident in 31 of the 63 cases (49%) with primary gastritis but in none of the 4 patients with secondary gastritis. This group is too small, however, to allow a valid comparison.

In 13 (42%) of the 31 patients with *C pylori* infection and in 7 (19%) of the 36 patients with no *C pylori,* gastric duodenal ulcers (or both) were noted endoscopically (Table 3). Overall, upper gastrointestinal ulcerations appeared more frequently in the presence of *C pylori* ($P<.04$, Fisher's exact test).

Comparison of Pediatric and Adult Patients

There was a higher prevalence of *C pylori* in adults (31/67 [46%]) than in children (4/17 [24%]) who required medical care for gastritis over the five-year study period. In those with no evidence of *C pylori,* however, a probable underlying cause of the gastritis was identified in 10 of 13 children but in only 4 of 67 adults. In the patients with primary gastritis, *C pylori* was present in 4 (57%) of the 7 children and in 31 (49%) of the 63 adults.

Discussion

Campylobacter pylori infection was found only in children and adults with primary gastritis. The 57% prevalence of the infection in children with primary gastritis is equivalent to the findings of Drumm and associates.[14,15] *C pylori* infection may cause most cases of hitherto-unexplained gastritis in children, although the direct cause and effect of the infection and the influence of other factors in the pathogenesis of gastritis in this age group remain to be studied. Conversely, most children with gastritis and no *C pylori* present on biopsy had predisposing conditions (10 of 13), in contrast to only 4 cases of secondary gastritis found among the 36 adults with gastritis and no *C pylori*. Although factors such as drug use, smoking, and alcohol ingestion may contribute to the findings in the adult group, these agents generally have not been proved to cause histologic evidence of gastritis.

TABLE 3.—*Location of Ulcers in Adult Patients With Gastritis*

Location	Campylobacter pylori on Biopsy, n=31, No.	No Campylobacter pylori, n=36, No.
Hiatus hernia	1	0
Stomach	2	1
Antrum	8	2
Duodenum	2	3
Antrum and duodenum	0	1
Total number of patients with ulcers	13	7

Infection with *C pylori* was associated with more active (acute) inflammatory changes in adults than in children. It was seen in children with chronic gastritis only, with an absence of polymorphonuclear leukocyte infiltrates, the marker for acute inflammation.[21] These findings are consistent with the histologic characteristics of the five pediatric cases of *C pylori*-associated gastritis described by Czinn and colleagues.[11] By comparison, Drumm and co-workers described mixed inflammatory infiltrates in children with *C pylori* but found no correlation of the infection with the degree of inflammatory activity.[14,15] In 23 of 31 of the adult patients with *C pylori* infection, the biopsy specimens showed acute and chronic inflammatory changes ("active chronic gastritis") (Figure 1). This contrasts with previous reports where no relationship was found between the severity of gastritis and *C pylori* infection[22-25] but supports other studies documenting a correlation of active chronic gastritis with infection with *C pylori.*[4,6,26-28] Thus, it remains unclear whether *C pylori* is a primary cause of gastritis or whether in some patients it infects an already inflamed mucosa.[28] More data are needed to compare the type and severity of gastritis in children and adults.

In this retrospective study the prevalence of *C pylori* in antral biopsy specimens showing inflammatory changes appears to have increased in 1987 compared with the previous four years. From 1983 through 1986, specimens from 55 antral biopsies were submitted for evaluation compared with 52 in 1987. Only 22% of those with gastritis (n=46) were found to have *C pylori* in the early period compared with 66% (n=38) in 1987. This finding may be biased due to an increasing number of antral biopsy specimens being obtained because of possible *C pylori.* The proportion of biopsy specimens with normal findings compared with the total number taken increased in the children in 1987 compared with that in 1983 through 1986 (Table 2), indicating a lower threshold for doing antral biopsies; this was unchanged in the adults. Also, the increased prevalence of *C pylori* is directly related to the cases of proven and primary antral gastritis. Further prospective studies are necessary to clearly determine whether the prevalence of *C pylori* infection is increasing or whether this observation is related to an enhanced medical awareness.

Clearly a limitation of our study is that only gastric antral biopsy specimens were examined. Although this species is most consistently found in the antrum,[1] it may be present exclusively in the body of the stomach.[29,30] Thus, our results

most likely underestimate the number of cases. *Campylobacter pylori* was detected in the antral biopsy specimen of 65% of our patients with upper gastrointestinal ulcers (Table 3). Rauws and associates examined four antral biopsy specimens per patient and found *C pylori* in 98% of ulcer patients.[6] An interesting finding was the association of *C pylori*-positive antral gastritis and an ulcer within a hiatus hernia in one patient.

Our data may suggest that the prevalence of *C pylori* infection increased in 1987, but more long-term retrospective and prospective studies should be done to examine whether the prevalence of the infection is increasing. Our findings indicate that *C pylori* infection is frequent in children with primary gastritis. Additional data on this infection in children and adults are needed to help define its pathogenesis, differences between age groups, environmental determinants, and regional variations.

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Strongyloidiasis Associated With Human T-Cell Lymphotropic Virus Type I Infection in a Nonendemic Area

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Concomitant strongyloidiasis and human T-cell lymphotropic virus type I (HTLV-I) infection has been reported from areas in Japan where both organisms are endemic. We present four cases of concomitant infection with these organisms from an area that is not endemic for Strongyloides stercoralis. *Three of the four patients had adult T-cell leukemia, an aggressive neoplasm resulting from HTLV-I infection, while the other was an asymptomatic carrier of HTLV-I. Three of the patients had spent their childhoods in an endemic location for both organisms, suggesting an initial infection at that time. Three patients were symptomatic from their parasitism. We conclude that strongyloidiasis may be found in nonendemic locations in patients with either adult T-cell leukemia or an asymptomatic HTLV-I carrier state. Whether infestation with this parasite contributes to the leukemogenesis of HTLV-I, as postulated by others, cannot at this time be determined.*

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Strongyloidiasis is an intestinal infection caused by *Strongyloides stercoralis.* Infection is thought to be acquired in most cases by transcutaneous penetration by the larvae, but in rare instances transmission by sexual contact or the ingestion of contaminated food may also occur.[1] The disease has a worldwide distribution, with a higher prevalence in tropical areas. It is found in 0.4% to 4% of residents in the southeastern United States and may also be found in rural areas and mental institutions.[2,3] In nonendemic locations, such as Hawaii, *S stercoralis* is most commonly found in immigrant populations.[4]

Clinical infection is usually characterized by chronic relapsing gastrointestinal symptoms including nausea, vomiting, dyspepsia, bloating, and diarrhea, although as many as a third of patients may be asymptomatic.[3] Long-standing carrier states are often observed, with the recovery of *S stercoralis* 20 to 30 years following a move away from the endemic site of the initial infection.[1,5] A syndrome of hyperinfection with disseminated disease and a high mortality rate may be encountered in immunocompromised hosts.[6-8]

Human T-cell lymphotropic virus type I (HTLV-I) is a human retrovirus that has been linked etiologically to adult T-cell leukemia (ATL), a neoplasm of T-cell origin. In Okinawa, a prefecture in southern Japan, a high prevalence of antibodies to HTLV-I has been found in patients with strongyloidiasis.[9] Conversely, in patients from Okinawa with HTLV-I infection, there is a significantly higher prevalence of *S stercoralis* carriers when compared to background population rates.[10]

To further understand the relationship between these organisms, we identified and retrospectively reviewed four cases of strongyloidiasis associated with either HTLV-I infection or ATL. These patients were unusual in that they all resided in Hawaii, an area previously shown to have a low prevalence of strongyloidiasis.[4]

Subjects and Methods

Patients were identified from either the hematology practice of one of us (J.M.N.) or from a retrospective review of clinical cases at the Kuakini Medical Center, Honolulu. The patients in cases 3 and 4 were not able to be tested for antibody to HTLV-I but were previously reported to have high-grade T-cell lymphomas, in one case consistent with ATL.[11]

The diagnosis of *S stercoralis* infestation was made on freshly collected specimens of either stool (cases 3 and 4), gastric aspirate (case 1), or postmortem histologic specimens of small bowel (case 2).

In cases 1 and 2, serum was studied by an enzyme-linked immunosorbent assay (ELISA) (Biotech Research Laboratories, Inc, Rockville, Md) for HTLV-I antibodies, and HTLV-I antibody positivity was confirmed by Western blot assay (Biotech Research Laboratories, Inc, Rockville, Md). All specimens were run in duplicate and under standard conditions.

Report of Cases

Case 1

A 71-year-old man of Japanese ancestry presented with dyspepsia, an 8-kg (18-lb) weight loss, Hemoccult-positive stools, hypoalbuminemia, and an elevated serum alkaline phosphatase level. Although born in Hawaii, he had lived in Okinawa from age 2 to age 19. He had otherwise been healthy except for a past episode of nephrolithiasis. An abdominal computed tomographic scan had been done and showed no abnormalities. An esophagogastroduodenoscopy

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ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia
ELISA = enzyme-linked immunosorbent assay
HTLV-I = human T-cell lymphotropic virus type I

revealed mild proximal duodenitis. Biopsy specimens from the involved mucosa showed mild focal villous atrophy, with a large amount of *Strongyloides stercoralis* present, including both filariform and rhabdoid larvae. The patient was treated with a course of thiabendazole, with subjective clinical improvement. He has since been found to be HTLV-I antibody-positive.

Case 2

The patient, a 68-year-old Hawaiian-born woman of Japanese ancestry, was seen because of lethargy, anorexia, weight loss, and fevers. On examination she had diffuse lymphadenopathy, and a subsequent biopsy specimen showed diffuse large-cell non-Hodgkin's lymphoma (T-cell immunoblastic sarcoma). She was found to have the antibody to HTLV-I by both ELISA and Western blot assay. She received several courses of chemotherapy consisting of BACOP (bleomycin sulfate, doxorubicin [Adriamycin] hydrochloride, cyclophosphamide, vincristine sulfate [Oncovin], and prednisone) and later M-BACOD (bleomycin, doxorubicin, cyclophosphamide, methotrexate, and dexamethasone), but her condition continued to deteriorate and she had recurrent infections. Hypercalcemia later developed, requiring the administration of plicamycin (previously called mithramycin) for its control. After a prolonged hospital course, she died of a *Staphylococcus aureus* pneumonia. An autopsy showed an aggressive T-cell immunoblastic sarcoma and clinically unsuspected parasitism of the small bowel with *S stercoralis.*

Case 3

The patient, a 58-year-old Japanese man who was initially seen in 1964 with weight loss, anorexia, and mild diarrhea, was found by examination of fresh stool to have *S stercoralis* infestation. He had been born in Okinawa but had later immigrated to Hawaii. He was initially treated with gentian violet but because he failed to improve, he was readmitted to hospital. On readmission, the patient was found to have spiking fevers, mild leukocytosis, and diffuse patchy infiltrates on a chest roentgenogram. A sputum specimen showed *S stercoralis,* and an upper gastrointestinal study disclosed a dilated duodenal bulb. In the hospital the patient had confusion from hypercalcemia, which was successfully managed with the use of corticosteroids. He subsequently died of complications related to a liver biopsy and acute renal failure. The necropsy report initially suggested a systemic inflammatory process of undefined origin; on review, however, the histologic examination showed a diffuse high-grade lymphoma (pleomorphic immunoblastic sarcoma, T-cell type).

Case 4

A 57-year-old Japanese man was admitted to our hospital in 1961 with anorexia, low-grade fevers, weight loss, and diffuse adenopathy. Born in Okinawa, he later immigrated to Hawaii. While in the hospital, a fresh stool examination showed *S stercoralis.* A lymph node biopsy specimen showed an acute lymphoma, diffuse type, and the patient was initially treated with mechlorethamine hydrochloride. He later died of this lymphoma. Retrospective review of the antemortem lymph node biopsy specimen revealed a high-grade lymphoma (pleomorphic immunoblastic sarcoma, T-cell type). No serum calcium levels were evaluated, and an autopsy was not done.

Results

The mean age of the four patients at the time the diagnosis of strongyloidiasis was established was 64 years. All four persons were known to have strongyloidiasis, three with gastrointestinal symptoms and one clinically unsuspected. The most common symptoms reported were anorexia, mild diarrhea, weight loss, and dyspepsia.

The diagnosis of strongyloidiasis was established from an examination of fresh stool in two patients and from gastric aspirate in one patient. The fourth patient (case 2), who remained asymptomatic from the standpoint of her strongyloidiasis, was found at autopsy to have a massive load of the parasite in her small bowel.

Three of the four patients had presumably acquired strongyloidiasis at an early age while living in Okinawa, an area endemic for *S stercoralis.* The fourth (case 2) had had no travel history to an area endemic for *S stercoralis.*

Two of the patients (cases 3 and 4) did not have documented HTLV-I infection, but because they were originally from Okinawa and appeared to have ATL, it is probable that they were carriers of HTLV-I. Unfortunately, family members are not available for testing. The other two patients had documented HTLV-I antibodies. One of these patients died of ATL (case 2), but the other remains asymptomatic from the standpoint of his HTLV-I infection (case 1). The latter could have acquired HTLV-I infection in Hawaii, from his Okinawan parents, or while living in Okinawa from age 2 through 19. One patient (case 2) appears to have acquired both HTLV-I and *S stercoralis* in Hawaii. She, too, is of Okinawan ancestry.

Hypercalcemia was present in two of the three patients with ATL. Both patients had symptoms attributed to hypercalcemia and required treatment to lower their serum calcium levels. The asymptomatic HTLV-I antibody-positive patient (case 1) did not have hypercalcemia.

A summary of the clinical characteristics of the four patients is given in Table 1.

Discussion

Human T-cell lymphotropic virus type I is a type C human retrovirus that was first identified by Poiesz and colleagues[12] in a patient with a cutaneous T-cell malignant neoplasm. It has since been found to be related etiologically to ATL, a T-cell malignant disorder often associated with an

TABLE 1.—*Characteristics of Patients With Strongyloidiasis and HTLV-I Infection or Adult T-cell Leukemia (ATL)*

Case	Age, yr	Sex	Birthplace	HTLV-I Status	ATL	Hypercalcemia	Symptoms
1	71	♂	Hawaii	Yes	No	No	Dyspepsia
2	68	♀	Hawaii	Yes	Yes	Yes	Asymptomatic
3	58	♂	Okinawa	Unknown	Yes	Yes	Anorexia, weight loss, mild diarrhea
4	57	♂	Okinawa	Unknown	Yes	No	Anorexia, weight loss, mild diarrhea

HTLV-I = human T-cell lymphotropic virus type I

aggressive clinical course, symptomatic hypercalcemia, and frequent cutaneous leukemia cell infiltrates. In addition, an asymptomatic carrier state, a preleukemic state (pre-ATL), and occasionally a chronic or smoldering form of ATL may also be observed in patients infected with the virus.[13] More recently, HTLV-I has also been associated with other syndromes, including tropical spastic paraparesis and possibly thrombotic thrombocytopenic purpura.[14-17]

The virus is found to be endemic in geographically restricted areas in southern Japan, the Caribbean islands, Africa, South America, and in the southeast United States. It has been found in as many as 9% of intravenous drug users in New York and, therefore, appears to be spreading in a population also at risk for acquiring human immunodeficiency virus infection.[13,18] Viral transmission occurs by several means, including sexual intercourse, the transfusion of contaminated cell-containing blood products, ingestion of breast milk from mothers who are virus carriers, and the sharing of contaminated needles by intravenous drug users. There is also familial clustering of HTLV-I, suggesting both horizontal and vertical transmission of the virus.[11,19,20]

Current estimates indicate that ATL will eventually develop in fewer than 0.2% of those infected.[21,22] Those carriers of the virus in whom adult T-cell leukemia has not yet developed are found to have polyclonal integration of HTLV-I proviral DNA in their lymphocytes. Once monoclonal integration of HTLV-I proviral DNA occurs, however, either pre-ATL, the smoldering or chronic form of ATL, or overt ATL is found.[10,13] The only clinical disorder known to occur while the virus is still integrated in a polyclonal fashion is tropical spastic paraparesis, and this appears to be rare.

It is well known that *S stercoralis* infestation is a chronic illness that, because of the organism's unusual life cycle, can persist with or without symptoms for many years after a person leaves an endemic area.[1,5] It is therefore probable that three of our patients may have been harboring *S stercoralis* since their childhoods in Okinawa. As noted, these three patients all had mild gastrointestinal symptoms, but a fourth patient was asymptomatic from the standpoint of her strongyloidiasis.

Studies from endemic areas have noted the coexistence of strongyloidiasis and ATL or HTLV-I infection.[9,23] In Okinawa, 60% of patients with strongyloidiasis were found to have HTLV-I antibody, compared with only 20% of those without strongyloidiasis.[9] Of 36 patients with both HTLV-I and strongyloidiasis, 14 (39%) were found to have monoclonal integration of HTLV-I proviral DNA in their lymphocytes.[10] In that study, monoclonality was associated with the presence of abnormal circulating lymphocytes, an increased CD4:CD8 ratio, clinically smoldering ATL, and somewhat more severe symptoms of strongyloidiasis.[10]

Several possibilities may explain the concurrent infection with these organisms. One is that infection with HTLV-I causes defective T-cell function and that the resultant cell-mediated immunodeficient state may predispose to both infection with *S stercoralis* and toward the progression of this infection to a hyperinfective stage.

Cell-mediated immunity has been found to be defective in patients with either an HTLV-I carrier state or ATL, and these patients may be at risk for several opportunistic infections, including *Pneumocystis carinii* pneumonia and disseminated fungal infections.[24-26] In addition, other studies have shown that patients with defective T-cell function are predisposed to strongyloidiasis and that pre-existing strongyloidiasis may be converted to a hyperinfective stage with the onset of another unrelated immunosuppressive disease.[7,8,27] We postulate that our patients with ATL or HTLV-I are more likely to acquire strongyloidiasis and if already infected with this organism, symptoms are more likely to develop that would lead to the diagnosis of parasitism.

Another explanation that has been suggested by a group of investigators in Okinawa[10,23] is that chronic infestation with *S stercoralis* may predispose to infection with HTLV-I and may act as a cofactor in the leukemogenesis of the virus. In the United Kingdom, studies of former Far East prisoners of war have shown that long-standing strongyloidiasis may cause generally impaired immunity and an increased risk of acquiring tuberculosis.[28] Whether these patients are also at an increased risk of acquiring retroviral disease has not been determined.

Those patients studied in Okinawa with concomitant HTLV-I and strongyloidiasis were more likely to have ATL than the group with only HTLV-I infection.[10] This has led these investigators to suggest *S stercoralis* as a possible cofactor in the leukemogenesis of HTLV-I.[10,23] Other organisms, including filariasis and malaria, have also been suggested as potential cofactors in the development of ATL.[29,30] It seems plausible that prolonged antigenic stimulation induced by chronic parasitic infection may lower a host's immune response, reactivating a latent virus infection with a progression of polyclonal to monoclonal T-cell proliferation. A better understanding of the factors influencing HTLV-I-related leukemogenesis is needed to further evaluate these hypotheses.

Although unlikely, it remains possible that *S stercoralis* itself may be a vector of HTLV-I. This has not yet been investigated.

We have described four patients with either an asymptomatic HTLV-I carrier state or ATL who have had concomitant strongyloidiasis. This had not previously been described in an area that is not endemic for *S stercoralis.* The persistent parasitism seen in these patients is not surprising in view of previous studies on migrant populations; in these patients, however, this may also reflect an immunosuppressant effect of HTLV-I infection or ATL. We suggest that those patients known to have HTLV-I infection or HTLV-I-associated disease should be screened closely for the development of symptoms suggestive of strongyloidiasis. Whether routine stool examinations should be done to screen for asymptomatic strongyloidiasis in HTLV-I-infected patients is not known at this time. We recommend further studies on both the role that persistent parasitism plays with respect to the leukemogenesis of HTLV-I and on the immunomodulating effect of this virus on the human host.

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Clinical Review

Long-term Anticoagulation
Indications and Management

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Each year half a million persons in the United States receive long-term anticoagulant therapy to prevent venous and arterial thromboembolism. Unfortunately, the relative benefits and risks of anticoagulant therapy have not been adequately quantified for many thromboembolic disorders, and the decisions as to whether, for how long, and how intensely to administer anticoagulation are often complex and controversial. Several expert panels have published recommendations for anticoagulant therapy for different thromboembolic disorders; the primary area of disagreement among these panels concerns the optimal intensity of anticoagulation. Recent research and analytic reviews have helped to clarify both the risk factors for and the appropriate diagnostic evaluation of anticoagulant-induced hemorrhage. Clinicians must be aware of the nonhemorrhagic complications of anticoagulant therapy, particularly during pregnancy. The administration of anticoagulants is difficult both in relation to dosing and long-term monitoring. Knowledge of the pharmacology of the anticoagulants, an organized approach to ongoing monitoring, and thorough patient education may facilitate the safe and effective use of these drugs.

(Stults BM, Dere WH, Caine TH: Long-term anticoagulation—Indications and management. West J Med 1989 Oct; 151:414-429)

About 500,000 persons annually in the United States receive anticoagulants for the treatment and prophylaxis of thromboembolic disorders.[1,2] The most common indications for long-term anticoagulant therapy in recent years have been venous thromboembolism, valvular heart disease (especially prosthetic heart valves), atrial fibrillation, and ischemic cerebrovascular disease.[3-5] Patients anticoagulated long term are usually middle-aged or elderly; in two recent series, their average age was 55 to 60 years, and 25% to 30% were older than 70 years.[4,5] They frequently have chronic illnesses in addition to their thromboembolic disorder; in one review of patients attending a university hospital anticoagulation clinic, 25% had three or more medical problems, and nearly 70% took three or more medications in addition to anticoagulants.[4] Anticoagulant therapy, especially in patients with coexisting chronic illness and taking several medications, is associated with considerable morbidity and some mortality from hemorrhage. As a result, the decision to anticoagulate an individual patient is often complex and sometimes controversial. Clinicians must attempt to estimate the benefit:risk ratio for each patient by considering the following variables[6]:

- The rate, morbidity, and mortality of thromboembolism without anticoagulation;
- The expected reduction in rate of thromboembolism with anticoagulation;
- The rate, morbidity, and mortality of anticoagulant-induced complications, especially hemorrhage;
- The following effects of anticoagulant therapy on a patient's quality of life:
  - The economic costs of medications, laboratory tests, clinic visits, and complications;
  - Any required alterations in life-style or occupation;
  - Anxiety that may be engendered in some patients by anticoagulant therapy.

Unfortunately, for most thromboembolic disorders, available data do not adequately quantify these variables. Moreover, the benefits and risks of anticoagulant therapy may vary considerably among different patients and in the same patient over time.[6]

Despite these uncertainties, clinicians must still decide whether and how to anticoagulate their patients. To facilitate making more rational clinical decisions, several groups of experts have recently analyzed the available evidence on the indications for and complications associated with long-term anticoagulant therapy.[7-12] We review their conclusions and recommendations, updating them when appropriate, and describe techniques for determining the optimal administration of anticoagulants. First, however, it is important to summarize the basic pharmacology and laboratory monitoring of anticoagulants.

Pharmacology and Laboratory Monitoring of Anticoagulants

The use of warfarin sodium, a vitamin K antagonist, leads to the synthesis of biologically inactive forms of clotting factors II, VII, IX, and X. The one-stage prothrombin time (PT) is sensitive to three of these four vitamin K-dependent factors and is used to monitor the effects of warfarin therapy. It may be expressed as the prothrombin time ratio: patient time in seconds per normal control time in seconds. The serum half-lives of these clotting factors vary from four to six hours for factor VII to two to three days for factors II and X. While large doses of warfarin may increase the PT ratio

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ABBREVIATIONS USED IN TEXT

ACCP = American College of Chest Physicians
DVT = deep venous thrombosis
INR = international normalized ratio
ISI = international sensitivity index
MI = myocardial infarction
NHLBI = National Heart, Lung, and Blood Institute
PT = prothrombin time
PTT = partial thromboplastin time
WHO = World Health Organization

within 24 hours due to a suppression of factor VII, maximal depression of the activities of factors II and X—and therefore the maximal antithrombotic effect—is delayed for as long as five to seven days.[13] Warfarin therapy also inhibits synthesis of the anticoagulant proteins C and S, which are important in preventing thrombosis on the surface of platelets and vascular endothelium.[13] Because protein C has a short half-life similar to that of factor VII, the first few days of warfarin therapy may theoretically constitute a period of relative hypercoagulability, as the anticoagulant activity of protein C decreases before the procoagulant activity of factors II, IX, and X. These events may have pathophysiologic importance for the rare complication of warfarin-induced skin necrosis discussed later.[14]

The use in North America and Europe of different thromboplastins to measure the PT ratio has resulted in some confusion.[2] Rabbit brain thromboplastins are used in most North American centers, and human brain thromboplastins have been used in Europe. Human brain thromboplastins are more responsive to the reduction in vitamin K-dependent clotting factors, resulting in a significantly greater PT ratio compared with that in the same plasma specimen tested with a rabbit brain preparation. To limit confusion, the World Health Organization (WHO) has recommended that all PT ratio measurements worldwide undergo a standard correction and be expressed during long-term maintenance therapy as the "international normalized ratio" (INR).[1,2] The INR is the PT ratio that would be observed if the plasma specimen were tested with the WHO reference thromboplastin originally derived from human brain. The PT ratio measured with any local thromboplastin can be converted to the corresponding INR using the equation: INR = observed PT ratio^{ISI}, where ISI is the "international sensitivity index" specific to the particular thromboplastin.[1] The ISI is a measure of the particular thromboplastin's responsiveness to the reduction of vitamin K-dependent coagulation factors. The WHO reference thromboplastin has an ISI of 1.0; the ISI increases as thromboplastins become less responsive. It has been proposed that all thromboplastin manufacturers calibrate their reagents against the WHO reference thromboplastin and provide local laboratories with the resulting ISI, so that they can express locally measured prothrombin time ratios as the international normalized ratio using a simple nomogram.[2,15] Most ISI values for rabbit brain thromboplastins in North America are between 2.0 and 2.6.[2] Table 1 lists the PT ratio ranges of rabbit brain thromboplastins with ISI values of 2.0, 2.3, and 2.6 along with the equivalent INR ranges. Few North American laboratories currently express PT ratios as the INR.[2] It is notable that the reliability of this system for converting locally measured PT ratios to the INR system during the first few weeks of coumarin drug administration has recently been questioned.[16] Subsequent PT ratios in this article are uncorrected measurements using a rabbit brain thromboplastin with an ISI of approximately 2.4, as recently used by a national task force on anticoagulation therapy.[8]

TABLE 1.—*Equivalent Prothrombin Time (PT) Ratios for North American Rabbit Brain and International Normalized Ratio (INR) Reference Thromboplastins**

	Corresponding Rabbit Brain PT Ratios		
INR	*ISI=2.0*	*ISI=2.3*	*ISI=2.6*
2.0-3.0	1.4-1.7	1.4-1.6	1.3-1.5
3.0-4.5	1.7-2.1	1.6-1.9	1.5-1.8

ISI=international sensitivity index

*Modified from Hirsh and Levine.[2]

Subcutaneous heparin may be used as an alternative to warfarin for long-term anticoagulation in selected patients with venous thromboembolism[17] and for pregnant women with prosthetic heart valves.[12] Heparin augments the inhibition by antithrombin III of several activated coagulation factors but has no effect on the production of these factors. Therefore, in contrast to those of warfarin, the antithrombotic effects of heparin occur immediately but also begin to decline about 12 hours or longer after cessation of subcutaneous administration, depending on the dose.[17] Heparin therapy is generally monitored by the activated partial thromboplastin time (PTT), although in selected patients measuring whole blood heparin levels with protamine titration may be helpful.[18]

Indications for Long-term Anticoagulation

Expert panels have recently published recommendations for anticoagulant therapy for thromboembolic disorders, including indications for use and the appropriate intensity and duration of therapy.[7-12] The recommendations of the task force of the American College of Chest Physicians (ACCP) and the National Heart, Lung, and Blood Institute (NHLBI), originally published in 1986[7] and updated with several modifications in 1989,[8] are reproduced in Table 2; they include an estimate of the relative strength of scientific evidence supporting each recommendation.

The primary controversy among the various expert recommendations relates to the intensity of anticoagulation for different thromboembolic disorders. The ACCP-NHLBI task force recommends the use of low-intensity warfarin to a PT ratio of 1.3 to 1.5—a prothrombin time of about 15 to 18 seconds—for all thromboembolic disorders except mechanical prosthetic heart valves, bioprosthetic mitral valves with associated atrial fibrillation or left atrial thrombi for the first three months after a valve replacement operation, and recurrent systemic embolism; for these disorders they suggest a conventional warfarin regimen to a PT ratio of 1.5 to 2.0—a prothrombin time of about 18 to 24 seconds. If there is no recurrence of systemic embolism after a year of warfarin therapy to a PT ratio of 1.5 to 2.0, those patients who do not have mechanical heart valves may have the intensity of warfarin therapy reduced to a PT ratio of 1.3 to 1.5; patients with mechanical heart valves should continue to receive conventional-intensity warfarin therapy. There is evidence from randomized, controlled trials supporting the efficacy of low-intensity warfarin for the treatment of venous thromboembolism after an initial course of heparin,[19] the prevention of cardioembolism during the first three months after bioprosthetic heart valve replacement,[20] and short-term (one month) prevention of cardioembolism and venous thrombo-

embolism following acute myocardial infarction.[21,22] In the two trials that directly compared the two intensities of anticoagulation, low-intensity warfarin therapy was associated with twofold[20] and fourfold[19] lower rates of hemorrhagic complications than conventional warfarin therapy. In contrast, evidence for the other recommendations in Table 2 for the use of either low- or conventional-intensity warfarin is considerably weaker, coming from nonrandomized trials, case studies, or both.[8] Pending further studies, some expert groups, therefore, recommend conventional-intensity warfarin therapy for all thromboembolic disorders other than venous thromboembolism.[10,12]

TABLE 2.—*Recommendations for Long-term Anticoagulation**

Thromboembolic Disorder	*Recommended Prothrombin Time (PT) Ratio*	*Duration of Therapy*	*Level of Evidence†*	*Comments*
Venous thromboembolism				
Proximal deep venous thrombus (DVT) or pulmonary embolus	1.3-1.5	3 months for first episode	Strong	More prolonged or lifetime anticoagulation may be required for recurrences or ongoing risk factors
Isolated symptomatic calf DVT	1.3-1.5	3 months for first episode	Weak	If anticoagulation is contraindicated, patients with isolated calf DVT may be monitored with serial noninvasive studies for proximal extension of clot
Chronic atrial fibrillation (AF)				
With cardioembolic stroke	1.5-2.0 for 1 year, then 1.3-1.5	Lifetime	Weak	
With valvular heart disease	1.3-1.5	Lifetime	Weak	
With idiopathic dilated and hypertrophic cardiomyopathies	1.3-1.5	Lifetime	Weak	
With thyrotoxicosis	1.3-1.5	Until euthyroid state and sinus rhythm restored for 2-4 weeks	Weak	
With coronary, hypertensive, or congenital heart disease, in *selected* patients, especially when complicated by heart failure	1.3-1.5	Lifetime	Weak	Because of limited data, decision to anticoagulate these patients must be carefully individualized; consider anticoagulation in presence of heart failure and in younger patients at low risk of hemorrhage
Idiopathic AF without associated heart disease (lone AF)				
Older than 60, *selected* patients	1.3-1.5	Lifetime	Weak	Only lone AF patients older than 60 have increased stroke risk; consider anticoagulation only if low risk of hemorrhage
Younger than 60	No therapy	...		
Cardioversion of atrial fibrillation	1.3-1.5	3 weeks before and 2-4 weeks after cardioversion	Weak	Anticoagulation not required for cardioversion of other atrial arrhythmias
Valvular heart disease				
Mitral regurgitation or stenosis				
With cardioembolic stroke	1.5-2.0 for 1 year, then 1.3-1.5	Lifetime	Weak	Anticoagulation not required for uncomplicated mitral valve prolapse or for isolated aortic valve disease or aortic bioprosthetic heart valves in presence of sinus rhythm; adding dipyridamole is optional for patients with mechanical prostheses but is indicated if systemic embolism recurs despite adequate warfarin therapy
With chronic or paroxysmal AF	1.3-1.5	Lifetime	Weak	
With enlarged left atrium (diameter >55 mm) and sinus rhythm	1.3-1.5	Lifetime	Weak	
Mitral valve prolapse				
With cardioembolic stroke	1.5-2.0 for 1 year, then 1.3-1.5	Lifetime	Weak	
With AF or recurrent transient cerebral ischemia refractory to aspirin therapy	1.3-1.5	Lifetime	Weak	
Mechanical prosthetic heart valves	1.5-2.0	Lifetime	Weak	
Bioprosthetic heart valves				
Mitral position, sinus rhythm	1.3-1.5	For first 3 months after replacement	Strong	
Mitral position with AF or left atrial thrombi	1.5-2.0 for first 3 months after replacement, then 1.3-1.5	Lifetime	Weak	
Acute myocardial infarction (MI)				
Transmural anterior acute MI,	1.3-1.5	For 3 months after acute MI	Strong	Indications for anticoagulation beyond 3 months are uncertain
or large inferior acute MI with heart failure or AF	1.3-1.5	For 3 months after acute MI	Weak	
After acute MI with severe heart failure, AF, or previous venous thromboembolism	1.3-1.5	Lifetime	Weak	
Idiopathic dilated cardiomyopathy	1.3-1.5	Lifetime	Weak	
Prevention of recurrent cardioembolism	1.5-2.0 for 1 year, then 1.3-1.5	Lifetime	Weak	After 1 year of therapy at PT ratio of 1.5-2.0, warfarin intensity can be reduced to a PT ratio of 1.3-1.5, if there have been no other recurrences

*Modified from American College of Chest Physicians and National Heart, Lung, and Blood Institute recommendations.[8]
†Strong=supporting evidence from randomized trials, weak=suggestive evidence from nonrandomized trials or uncontrolled case studies.

Venous Thromboembolism

Deep vein thrombosis and pulmonary embolism. Without a course of long-term anticoagulation following inpatient heparin therapy, the recurrence rate of proximal deep venous thrombosis (DVT) (popliteal vein and above) over the next three months is nearly 50%, as compared with 2% to 4% in therapeutically anticoagulated patients.[23] In one randomized trial, a three-month course of low-intensity warfarin therapy (PT ratio of 1.3 to 1.5) was shown to be as effective as a conventional warfarin regimen (PT ratio of 1.5 to 2.0) in preventing recurrent venous thromboembolism in patients with proximal DVT; the low-intensity regimen, however, was associated with a fourfold lower rate of hemorrhagic complications—5% versus 20%.[19] The subcutaneous administration of heparin every 12 hours in a dose sufficient to prolong the activated partial thromboplastin time to 1.5 times the control value six hours after a dose is as effective and safe for proximal DVT as the low-intensity warfarin regimen, although somewhat more expensive and inconvenient.[17,24] This regimen, sometimes referred to as "adjusted-dose" subcutaneous heparin therapy, may be useful for patients with contraindications to warfarin, including pregnancy, warfarin allergy, a history of warfarin-induced skin necrosis, or an inability to have regular monitoring of the prothrombin time ratio. Although definitive trials have not been done, the ACCP-NHLBI panel also recommends low-intensity warfarin therapy for patients with pulmonary embolism. Others suggest more intense anticoagulation to a PT ratio of 1.5 to 1.8 for patients with pulmonary emboli.[25(p1587)]

The optimal duration of anticoagulation for patients with proximal DVT and pulmonary emboli is unknown. The recommendations for treating a first episode vary from 1 to 12 months[26,27]; some clinicians empirically anticoagulate patients with pulmonary emboli longer than those with deep venous thrombi.[25] A recent retrospective analysis of patients with DVT or pulmonary emboli[28] and one randomized trial of patients with DVT[29] did not find higher rates of recurrent venous thromboembolism in patients anticoagulated four to six weeks as compared with patients treated as long as six months or more. A large randomized trial comparing one month and three months of anticoagulation is currently underway in the United Kingdom.[27] Pending further studies, the ACCP-NHLBI panel recommends that patients with DVT and those with pulmonary emboli with either no or transient risk factors for venous thromboembolism—such as the postoperative state, immobilization, previous estrogen therapy—receive three months of anticoagulation following a first episode. Patients with permanent risk factors, particularly malignant tumors and hereditary hypercoagulable states, should generally receive lifetime anticoagulation. Following the cessation of anticoagulation for a first episode of venous thromboembolism, the one-year recurrence rate is between 4% and 12%.[26] Unfortunately, patients at high risk for recurrence cannot yet be prospectively identified. How long to anticoagulate patients with recurrent venous thromboembolism is also uncertain, although their risk for yet another recurrence following three months of therapy may be 20% or greater.[30,31] For patients with recurrent venous thromboembolism but no other apparent risk factors, some clinical experts recommend anticoagulation for one year for a first recurrence and lifetime anticoagulation for any subsequent recurrences.[30] Another group that recommends anticoagulation for one month for an initial episode suggests three months of therapy for the first recurrence and lifelong treatment of repeated episodes.[27]

The management of isolated calf DVT is controversial.[26,32,33] With this disorder, pulmonary emboli, and especially fatal pulmonary embolism, are much less common than with proximal deep venous thrombi but do occur in a small but uncertain fraction of patients.[32-34] Untreated, 20% to 30% of cases of calf DVT extend proximally, usually during the first week after the onset of symptoms, increasing the risk of pulmonary emboli and chronic venous insufficiency.[26] In a study of patients with venographically confirmed calf DVT, failure to provide at least a six-week course of anticoagulation following intravenous heparin therapy resulted in a 30% recurrence rate of venous thromboembolism, including proximal DVT and pulmonary emboli.[35]

These results contrast with two recent prospective trials of nearly 1,000 patients with clinically suspected DVT evaluated with serial impedance plethysmography.[36,37] Optimally done, this procedure can detect proximal DVT with greater than 90% sensitivity and specificity.[38] In these two studies, when initial impedance plethysmography and serial follow-up impedance plethysmography on days 2, 5, and 10 showed no evidence of clot extension into proximal veins, it proved safe to withhold anticoagulant therapy. Based on these considerations, either therapeutic strategy may be applied to patients with calf deep venous thrombi.[26,32,33] If, however, serial impedance plethysmography or an accurate alternative noninvasive diagnostic test such as real-time B-mode ultrasonography[39] is either unavailable or not of locally validated accuracy, patients with calf DVT confirmed venographically should receive intravenous heparin for seven days followed by low-intensity warfarin or adjusted-dose subcutaneous heparin for three months.[8]

Atrial Fibrillation

About 15% of all ischemic strokes and 36% of ischemic strokes in persons older than 80 are associated with atrial fibrillation.[40,41] Some 2% to 5% of persons older than 65 have atrial fibrillation, and their lifetime risk of stroke is estimated at 35%[40]; 50% of these strokes result in disability or death.[42(p120)] The fraction of these strokes due to cardioembolism, as opposed to coexisting cerebrovascular disease, is unknown. Estimates range from 19% to 80%, but most recent estimates are from 50% to 70%.[40,43]

The risk of stroke appears to vary among different clinical subgroups of patients with atrial fibrillation (Table 3).[40] The highest annual risk is in those patients with either a previous clinical stroke or rheumatic valvular disease, particularly mitral stenosis. Patients with atrial fibrillation who have nonvalvular heart disease due to cardiomyopathy, coronary artery disease, hypertension, thyrotoxicosis, or congenital abnormalities have an intermediate risk of stroke, especially if there is substantial concurrent left ventricular dysfunction.[40,44-46] Patients younger than 60 with nonvalvular heart disease and paroxysmal atrial fibrillation and patients older than 60 with idiopathic atrial fibrillation without associated heart disease ("lone atrial fibrillation") also have an intermediate risk of stroke.[40,47] In contrast, patients younger than 60 with lone atrial fibrillation appear to be at a low risk for stroke.[40,48] The role of other possible risk factors for stroke in these patients (see Table 3) has not yet been adequately delineated.[40]

The benefit:risk ratio for anticoagulation in each of the

TABLE 3.—*Estimated Annual Stroke Risk in Subgroups of Patients With Atrial Fibrillation (AF)**

Degree of Risk	*Annual Stroke Risk, %*
High Risk	
Prior stroke	10-20
Rheumatic mitral valvular disease	4-6
Intermediate Risk	
Nonvalvular heart disease with left ventricular dysfunction	2-5
Paroxysmal AF, younger than 60	2.5
Lone AF, older than 60	2-3
Low Risk	
Lone AF, younger than 60	<0.5
Uncertain Risk	
Recent-onset versus chronic AF	
Paroxysmal versus chronic AF, older than 60	
Variation in risk according to cause of AF	
Associated carotid artery disease	
Previous asymptomatic stroke on computed tomography	
Echocardiographic features	
Left atrial size	
Ventricular function	
Mitral regurgitation	
Left atrial thrombi	
Other	

*Modified from Halperin and Hart[40] and from Hart,[42] Brand et al,[47] Kopecky et al,[48] and Dunn et al.[49]

different clinical subgroups of patients with atrial fibrillation is currently not known. On the basis of considerable retrospective evidence and the high incidence of embolic events in untreated patients, the ACCP-NHLBI panel recommends long-term anticoagulation, if not otherwise contraindicated, for patients with the following: a previous clinical stroke thought to be cardioembolic in origin; mitral valve disease and either chronic or paroxysmal atrial fibrillation; idiopathic dilated or hypertrophic cardiomyopathy; and thyrotoxicosis, until a euthyroid state and sinus rhythm have been restored for two to four weeks.[49] Patients with atrial fibrillation who have had a stroke should receive warfarin therapy to a PT ratio of 1.5 to 2.0 for a year; if there are no recurrences, a low-intensity regimen of warfarin to a PT ratio of 1.3 to 1.5 may be substituted thereafter. Low-intensity warfarin therapy is recommended for the other clinical subgroups.

Coronary and hypertensive heart disease account for 50% to 80% of cases of atrial fibrillation.[49] The efficacy and safety of long-term anticoagulation for these patients, most of whom are elderly, have not been determined. The results of two uncontrolled, retrospective studies of anticoagulation therapy for nonvalvular atrial fibrillation are directly contradictory.[50,51] It must also be remembered that the annual incidence of cerebral hemorrhage and major non-nervous system hemorrhage may be as high as 1% and 3%, respectively, when elderly patients are anticoagulated.[40] Because of this uncertainty, and pending the results of seven prospective clinical trials currently in progress,[40] the ACCP-NHLBI panel recommends that therapeutic decisions be carefully tailored to each patient in these subgroups of patients with atrial fibrillation. Long-term anticoagulation to a PT ratio of 1.3 to 1.5 may be cautiously considered in atrial fibrillation patients with coronary artery disease, hypertensive heart disease, and congenital heart disease, particularly if they are younger patients at low risk for hemorrhage or if there is complicating congestive heart failure. Low-intensity warfarin therapy may also be considered for some patients older than 60 who have lone atrial fibrillation. Patients younger than 60 with this disorder do not require anticoagulation.[40,49]

Since the publication of these recommendations, the results of the first randomized trial of anticoagulation for patients with chronic, nonrheumatic atrial fibrillation have been released.[52] In this Danish study of 1,007 patients with chronic atrial fibrillation with a median age of 74.2 years, conventional-intensity warfarin therapy (INR of 2.8 to 4.2) for two years significantly reduced vascular mortality and decreased the annual incidence of arterial thromboembolism from 5.5% to 2.0%, as compared with aspirin therapy, 75 mg a day, and with placebo; there were no fatal bleeding complications, and the two-year incidence of nonfatal hemorrhage was 7% in the warfarin group.[52] Firm recommendations must await the results of the other six prospective clinical trials.

Without anticoagulation, the incidence of systemic embolism following electrical or chemical cardioversion of atrial fibrillation has varied from 1% to 5% in different studies.[53] There is limited evidence that previous anticoagulation with low-intensity warfarin therapy may reduce this incidence to below 1%.[54] The duration of fibrillation necessary for thrombus to form within the left atrium is unknown; the ACCP-NHLBI panel recommends anticoagulation before cardioversion if fibrillation has been present three or more days,[49] but others would withhold anticoagulation for atrial fibrillation present for seven days or less, unless there is coexistent mitral valve disease.[55] The ACCP-NHLBI panel recommends anticoagulation with low-intensity warfarin therapy for three weeks before elective cardioversion to allow any thrombus present to become adherent to the atrial wall; others suggest anticoagulation to a PT ratio of 1.5 to 2.0.[12] Despite the restoration of a sinus rhythm, emboli may appear as long as three weeks after cardioversion, presumably due to a delay in the resumption of mechanical atrial contraction. Therefore, anticoagulation should be continued for two to four weeks following elective cardioversion.[49] When emergency cardioversion is required and previous anticoagulation is not feasible, low-intensity warfarin therapy should be initiated on the day of cardioversion and continued for two to four weeks if atrial fibrillation has been present three or more days or in the presence of mitral valve disease or a history of systemic embolism.[49] Emboli are rare following cardioversion of other atrial tachyarrhythmias, and prophylactic anticoagulation is generally not indicated.[49]

Valvular Heart Disease

Native mitral and aortic valvular disease. Because of design limitations in available studies, the actual incidence of systemic embolism in valvular heart disease is uncertain.[12] The annual incidence of systemic embolism is estimated at 1% to 5% for patients with mitral stenosis and 1% to 3% for patients with mitral regurgitation.[12] The most important risk factors for embolism are a history of embolism and coexistent chronic or paroxysmal atrial fibrillation; as many as 80% of patients with emboli have atrial fibrillation, and two thirds of these emboli occur in the first year after the fibrillation starts.[12] While left atrial enlargement may not be an independent risk factor for embolism, patients with pronounced left atrial enlargement—greater than 55 mm diameter on an echocardiogram—are at a high risk for atrial fibrillation and,

therefore, for embolism.[56] Considerable retrospective evidence suggests that anticoagulation prevents recurrent embolism in these patients and, by extension, likely will prevent initial embolism as well. The ACCP-NHLBI panel recommends that patients with mitral valve disease and systemic embolism receive warfarin therapy to a PT ratio of 1.5 to 2.0 for at least a year following the embolism, when the PT ratio may be reduced to 1.3 to 1.5. Patients with no previous embolism but with chronic or paroxysmal atrial fibrillation and those in sinus rhythm with marked left atrial enlargement should receive low-intensity warfarin.[56] Some clinicians also advocate anticoagulation for patients in sinus rhythm who have mitral valve disease with severe left ventricular dysfunction, and conventional rather than low-intensity warfarin therapy is recommended.[12]

The maximal incidence of stroke and transient ischemic attack in patients with mitral valve prolapse is estimated at 1 per 6,000 per year.[56] Asymptomatic patients with mitral valve prolapse who are in sinus rhythm thus require no treatment. Administering aspirin, 325 to 1,000 mg a day, is recommended for patients with mitral valve prolapse who have otherwise unexplained transient ischemic attacks.[12,56] Long-term warfarin anticoagulation is recommended by the ACCP-NHLBI panel for those patients who have recurrent transient ischemic attacks despite aspirin therapy (PT ratio of 1.3 to 1.5), with chronic or paroxysmal atrial fibrillation (PT ratio of 1.3 to 1.5), and for those with a previous stroke (PT ratio of 1.5 to 2.0 for a year, then a PT ratio of 1.3 to 1.5).[56] Others suggest a PT ratio of 1.5 to 2.0 for all these indications.[12]

In the absence of atrial fibrillation or a previous embolism, patients with isolated aortic valve disease do not require long-term anticoagulation.

Prosthetic heart valves. Without anticoagulation, patients with mechanical prosthetic heart valves have a 5% to 25% annual risk of systemic embolism; this can be reduced to 1.2% to 2.5% per year with a warfarin regimen to a PT ratio of 1.5 to 2.0.[57,58] The addition of dipyridamole—5 to 6 mg per kg of body weight per day—to warfarin therapy may further reduce the incidence of systemic embolism.[12,59] When warfarin therapy to a PT ratio of 1.5 to 2.0 is contraindicated, low-intensity warfarin in combination with dipyridamole may be used instead.[12] The embolic risk depends on the location of the prosthesis, the adequacy of anticoagulation, and possibly on the type of prosthesis. The risk of embolism is twofold greater with mitral and combined mitral and aortic prostheses than with an isolated aortic prosthesis.[12,57] Inadequate anticoagulation—defined as 25% or more of measured prothrombin time ratios of less than 1.5—increases the incidence of thromboembolism two to six times[57]; in one study of patients with mechanical valves, 30% of measured PT ratios were less than 1.5.[12,59] The St Jude Medical valve may have a lower incidence of systemic embolism than the Starr-Edwards and Bjork-Shiley valves.[12,58] A recent study found that low-intensity warfarin therapy resulted in an acceptably low annual incidence of systemic embolism in patients with St Jude valves.[60] Further confirmation of this finding is needed, however.

Bioprosthetic valves have a lower incidence of systemic embolism than mechanical valves.[12] Mitral bioprostheses carry the greatest risk, which without anticoagulation ranges from 1% per year for patients in sinus rhythm to 5% per year for patients with chronic atrial fibrillation or a left atrial thrombus noted at the surgical procedure.[12,61] The period of greatest risk is the first three months following the valve replacement, when 25% of all embolic events occur.[12] The ACCP-NHLBI panel recommends that all patients with mitral bioprostheses, and optionally those with aortic bioprostheses, receive warfarin for the first three months after surgical therapy. A recent randomized, controlled trial has shown that low-intensity warfarin therapy is as effective for these patients as conventional warfarin therapy and is associated with a twofold lower incidence of hemorrhagic complications.[20] Patients at a higher risk of embolism because of chronic atrial fibrillation or left atrial thrombi should receive warfarin therapy to a PT ratio of 1.5 to 2.0 for the first three months after the operation; the ratio may be reduced to 1.3 to 1.5 thereafter and the therapy continued indefinitely.[61]

Acute Myocardial Infarction

The use of anticoagulants in survivors of an acute myocardial infarction (MI) has long been controversial. Anticoagulants have been considered for these patients to prevent the following complications: recurrent acute MI, venous thromboembolism, systemic embolism from left ventricular mural thrombi, early recurrence or extension of an acute MI following thrombolytic therapy, and restenosis following coronary angioplasty.[12]

Most prospective trials of both short-term[21,22,62] and long-term anticoagulation[63-65] of survivors of acute MI have not shown a significant reduction in case-fatality rates. Two recent trials, however, have shown improved survival. In the Sixty Plus Reinfarction Study, conventional-intensity warfarin therapy for patients older than 60 at least six months after an acute MI reduced the incidence of fatal and nonfatal acute reinfarction by 55% over two years[66]; but there are some concerns about the methodologic validity of some aspects of the study.[12,67] In a recent Italian study, the use of subcutaneous calcium heparin, 12,500 units once a day, reduced mortality and reinfarction rates over eight months by 48% and 63%, respectively, in patients aged 50 to 75 years 6 to 18 months after an acute MI.[68] Still, pending further studies, most expert panels recommend giving only aspirin, 325 mg daily, as antithrombotic therapy for the prevention of reinfarction.[8,12]

Venous thromboembolism is adequately prevented by early mobilization and the administration of subcutaneous heparin, 5,000 to 7,500 units every 12 hours, until the patient is fully ambulatory.[12,67,69] One expert panel limits the use of subcutaneous heparin to high-risk patients: older than 70 years, a history of heart failure, immobile for longer than three days, obese, or a history of deep venous thrombosis or pulmonary embolism.[12]

Without anticoagulation, cerebral embolism occurs in 2.5% of all patients with an acute MI, 6% of patients with anterior MI, and about 10% of patients with an acute MI in whom echocardiography documented left ventricular mural thrombi.[12,67,70] The vast majority of these emboli emanate from left ventricular mural thrombi that can be shown in 30% to 40% of patients with transmural anterior acute MI but occur rarely with acute infarction at other sites.[67,71] The risk of embolism peaks at the end of the first week after an acute MI, with more than 70% of emboli occurring in the first month.[12,71] Although studies using serial echocardiograms show that only 20% to 40% of left ventricular mural thrombi will resolve spontaneously in the first 12 months after an

acute MI,[72] the embolic risk is generally thought to decline to very low levels by 8 to 12 weeks after the infarction.[12,67,73] (Dissenting data about the embolic risk of chronic left ventricular mural thrombi have recently been presented.[72,74]) Aside from the anterior site of an acute MI, risk factors for embolization have not been fully characterized but may include coexisting heart failure, atrial fibrillation, age older than 68 years, and the echocardiographic appearance of the left ventricular mural thrombi (specifically, the presence of pedunculated and mobile edges).[67,71] In prospective studies carried out 15 and 20 years ago, anticoagulation initiated shortly after admission to hospital with full doses of intravenous heparin and followed by low-intensity warfarin therapy for one to three months was shown to reduce the incidence of cerebral embolism by 25% to 75%.[21,22] More recent data suggest that anticoagulant therapy in the first 12 months following an acute MI increases the rate of resolution of left ventricular mural thrombi from between 20% and 40% to between 42% and 88%[70,72,75,76]; these studies are not of sufficient size to show a change in the rate of cerebral embolism. Aspirin and dipyridamole therapy, even when initiated within 12 hours of the start of an MI, does not reduce the incidence of left ventricular thrombous formation.[77] Therefore, prompt anticoagulation with therapeutic intravenous heparin followed by low-intensity warfarin therapy should be strongly considered for all patients with a transmural anterior wall acute MI and for large inferior wall acute MIs complicated by heart failure, atrial fibrillation, or apical dyskinesis or akinesis.[8,12] The absence of left ventricular mural thrombi on two-dimensional (2-D) echocardiography cannot be used at this time to decide not to anticoagulate patients with an acute MI.[12,67,71] 2-D Echocardiography fails to show as many as 20% of left ventricular mural thrombi, and although small studies suggest the incidence of embolism is low when left ventricular thrombi cannot be detected,[71,75] this has not been conclusively proved.

There are insufficient data about both the risk of embolism and the efficacy of anticoagulation for left ventricular mural thrombi persisting beyond three months after an acute myocardial infarction. Only 30% of these long-term thrombi resolve spontaneously over a two-year follow-up period; the others do not change in size, shape, or mobility.[72] Retrospective studies suggest that the risk of embolism is minimal beyond three months.[73] Recent small prospective studies from one institution, however, have noted a 14% incidence (life-table analysis) of systemic emboli in the two-year period following the echocardiographic detection of chronic left ventricular mural thrombosis in patients who have had an acute MI and who have a mean left ventricular ejection fraction of less than 35%.[72,74] While long-term warfarin therapy may double the rate of resolution of chronic left ventricular mural thrombi,[72,76] it is not known whether this treatment will result in a reduced incidence of cerebral embolism. No firm recommendations about anticoagulation beyond three months after an acute MI can be made at this time; a randomized clinical trial to answer this question may be useful.[72]

Following successful thrombolytic therapy for an acute MI, the rate of coronary reocclusion is 5% to 20%.[78] The optimal antithrombotic regimen to reduce this incidence has not yet been determined.[12] There is some evidence that aspirin treatment during the first five weeks (at least) following thrombolysis may help prevent coronary reocclusion,[79] and there is a clinical impression by some investigators that short-term treatment with therapeutic intravenous heparin may also be beneficial.[78] At the Second ACCP Conference on Antithrombotic Therapy, it was strongly recommended that aspirin, 160 to 325 mg, be given as soon as acute MI is clinically suspected and this regimen continued daily thereafter. Because of limited evidence, no recommendations were made for or against anticoagulant therapy.[8] Pending the completion of ongoing studies, some clinicians recommend giving therapeutic intravenous heparin combined with a low-dose regimen of aspirin—80 mg a day—for the first five days after thrombolysis followed by another five days of the same aspirin dosage and subcutaneous heparin, 10,000 to 12,500 units every 12 hours.[12,78] Subsequently, if surgical revascularization or coronary angioplasty is not done, patients at low risk for reocclusion may be treated long term with the use of aspirin alone, 160 to 325 mg a day.[78] For patients at high risk of reocclusion due to substantial residual coronary artery stenosis, residual thrombi, or recurrent ischemia, they empirically recommend a four- to six-week course of conventional-intensity warfarin combined with low-dose aspirin, 80 mg a day.[12,78]

The rate of restenosis following coronary angioplasty is 30% to 40% after six months.[80] Placebo-controlled trials of medical treatment to prevent restenosis have not yet been published. Several groups tentatively recommend antiplatelet therapy with aspirin, 325 mg three times a day, and dipyridamole, 75 mg three times a day, initiated one day before angioplasty and continued for six months[12,80]; a placebo-controlled trial of this regimen is underway.[12] Two trials with relatively small numbers of patients have not found warfarin therapy to be more effective than using either aspirin[81] or calcium channel blockade[82] in preventing recurrent symptoms or angiographic restenosis following coronary angioplasty.

Cardiomyopathies

Patients with idiopathic, dilated cardiomyopathy have cumulative incidences of systemic embolism and pulmonary embolism of 10% to 20% (3.5% annually) and 5% to 10%, respectively.[12] A patient's particular cardiac rhythm, degree of hemodynamic compromise, and the presence or absence of left ventricular mural thrombi on an echocardiogram do not clearly influence the risk of embolism.[12,49] Although no prospective, randomized trials are available, limited retrospective and uncontrolled data suggest a significant reduction in systemic and venous thromboembolism when conventional-intensity warfarin therapy is initiated shortly after diagnosis.[83,84] Currently the ACCP-NHLBI task force recommends low-intensity warfarin therapy for these patients.

Patients with hypertrophic cardiomyopathy who also have paroxysmal or chronic atrial fibrillation have an increased risk of systemic embolism at a rate of 2.4% per patient-year of follow-up.[49] Prophylaxis with low-[49] or conventional-intensity[85] warfarin therapy should be considered for them.

The incidence of systemic embolism and the indications for long-term anticoagulation in patients with dilated left ventricles from ischemic heart disease are not known.[85] Firm recommendations cannot be made at this time.

Cerebral Ischemia

When compared in controlled studies with no treatment, the use of placebo, or platelet antiaggregant therapy, anticoagulation has not significantly reduced morbidity or mor-

tality following either transient ischemic attacks or completed thrombotic stroke.[70,86,87] In contrast, when compared with that of placebo, the use of aspirin, 325 to 1,300 mg a day, reduces the incidence of stroke and death in both patient groups[88]; the most appropriate dose for aspirin prophylaxis, however, and the magnitude of its benefit remain controversial.[87,89,90] Because of methodologic limitations in the design and analysis of the earlier studies of anticoagulant therapy and variations in the intensity of anticoagulation prescribed, further well-designed clinical trials are needed comparing the use of warfarin with that of aspirin for stroke prophylaxis before a definitive recommendation can be made.[87] Meanwhile, if aspirin therapy or possibly carotid endarterectomy (or both) are ineffective or contraindicated for patients with recurrent transient ischemic attacks, some neurologists empirically recommend warfarin anticoagulation for three to six months, provided there are no contraindications.[88]

The management of acute cardioembolic stroke is complex and controversial and beyond the scope of this survey; it is thoroughly reviewed in recent publications.[70,87,88,91] There is evidence from randomized and nonrandomized studies that therapy with intravenous heparin followed by long-term warfarin anticoagulation to a prothrombin time ratio of 1.5 to 2.0 reduces the incidence of recurrent cardioembolic stroke by 66%.[88] The ACCP-NHLBI panel recommends warfarin therapy to a PT ratio of 1.5 to 2.0 for a year, after which, if there have been no recurrences, the intensity of anticoagulation may be reduced to a PT ratio of 1.3 to 1.5.[70]

Anticoagulant Use in Pregnancy

Anticoagulants are most frequently used in pregnancy for the treatment and prevention of venous thromboembolism and to prevent systemic embolism or valve thrombosis or both in patients with native valvular heart disease or artificial heart valves.[92] Unfortunately, there are few controlled data concerning either the efficacy or toxicity of anticoagulants during pregnancy; most published studies are retrospective series and case reports.[92] As a result, there is no consensus as to optimal management.[12,92-97] Further clinical trials are clearly needed.

Warfarin crosses the placenta freely. It is a teratogen in the first trimester, although estimates of the rate of embryopathy vary from less than 5%[94] to 30%.[97] Warfarin exposure in the second and third trimesters may result in a 3% incidence of central nervous system abnormalities including mental retardation or blindness, probably caused by fetal intracerebral hemorrhage.[93] Warfarin therapy increases the risk of fetal intracranial hemorrhage at delivery and of severe maternal hemorrhage in the event of unexpected obstetric complications—such as urgent cesarean section or abruptio placentae.[94,97] In contrast, heparin does not cross the placenta, and there is no convincing evidence that it is teratogenic.[92,94] Although retrospective studies have linked the use of heparin to increased fetal wastage,[98] many experts think these complications were caused by coexisting maternal disorders.[92,94-96] Excluding from these studies pregnant women with selected comorbid conditions decreases the rate of fetal complications in heparin-treated patients to levels similar to those in a healthy population not receiving heparin.[92,96] Prolonged heparin therapy in pregnancy may cause maternal bleeding and bone demineralization. In one study of 87 patients treated with adjusted doses of subcutaneous heparin, the risk of bleeding complications was 0% during the pregnancy and 9% in the postpartum period.[96] The risk for osteoporosis developing with long-term heparin therapy is unknown. A few cases of vertebral and rib fractures have been described in patients who took less than 10,000 to 20,000 units of heparin per day for three or more months.[94] Subclinical bone demineralization in pregnancy has been described with doses of 20,000 units per day given longer than 20 weeks,[99] but the significance of this finding is unknown; there is limited evidence that the demineralization may be reversible.[100]

For most patients, acute venous thromboembolism during pregnancy should initially be treated with seven to ten days of intravenous heparin, maintaining the activated partial thromboplastin time at 1.5 to 2.0 times control.[92] The most appropriate regimen for subsequent anticoagulation of these patients during pregnancy, and for pregnant patients with artificial heart valves, is controversial. Several groups recommend using adjusted-dose subcutaneous heparin throughout pregnancy for both groups of patients, maintaining the mid-dosing interval activated PTT at 1.5 to 2.0 times control.[12,92,93] Others think that the toxicity of warfarin therapy during the second and third trimesters has been overestimated but that the efficacy of adjusted-dose subcutaneous heparin therapy for patients with artificial heart valves has not yet been adequately shown. They recommend the use of adjusted-dose heparin in the first trimester and again after the 35th week of gestation; conventional-intensity warfarin is used from the 13th to 36th weeks.[94,95] High-risk patients with recent venous thromboembolism or artificial heart valves may be electively admitted a week before delivery and treated with intravenous heparin until the induction of labor.[12,93] The use of intravenous or adjusted-dose subcutaneous heparin and warfarin is started several hours after delivery, and the heparin therapy is discontinued after five to seven days when the desired prothrombin time ratio is attained. For patients with venous thromboembolism, anticoagulation should be continued for at least two to six weeks after delivery because of the high risk of recurrence in the puerperium.[92] Heparin and warfarin do not reach significant levels in breast milk and may be safely used by nursing mothers.[12,94,101] Some clinicians do recommend either doing a single, confirmatory PT ratio in the infant once the lactating mother's PT ratio is therapeutic[12] or providing the infant with vitamin K prophylaxis.[93]

The optimal management scheme during pregnancy for women with a history of venous thromboembolism has not been determined, and various regimens have been proposed.[92-94,97] Some clinicians reserve antenatal heparin prophylaxis for women with multiple recurrences or hereditary hypercoagulable disorders.[94] Others would provide prophylaxis for a single, previous, objectively documented episode of venous thrombosis using low-dose heparin, 5,000 units given subcutaneously every 12 hours until the middle of the third trimester, and then adjusted-dose subcutaneous heparin until delivery.[92,93] All recommend anticoagulant prophylaxis for at least two to six weeks after delivery.

Management of Long-term Anticoagulated Patients in the Perioperative Period

If anticoagulation is not discontinued before a major invasive operation, the incidence of serious perioperative bleeding is 13% to 45%.[102,103] For most patients with mechanical prosthetic heart valves, stopping warfarin therapy

two to three days preoperatively, such that the PT at the time of the operation is prolonged no more than 20% above the control value, and restarting it on the second postoperative day, results in a low incidence of both thromboembolic complications and hemorrhage.[103,104] Some clinicians empirically recommend the use of either low-molecular-weight dextran[105(p1699)] or dipyridamole[106(p1920)] for the first several postoperative days in these patients. Patients with mechanical mitral prostheses or previous systemic embolism may be at higher risk—5% to 20%—of cerebral emboli if perioperative anticoagulation is totally discontinued.[102,107] In these patients warfarin therapy may be discontinued three to five days before the surgical procedure with the substitution of therapeutic (activated PTT 1.5 times control) intravenous heparin until six hours before the operation. Therapy with intravenous heparin and oral warfarin may be restarted 24 to 48 hours after the operation, continuing the heparin for three to four days until the PT ratio is therapeutic.[105,107] Patients anticoagulated long term for indications other than prosthetic heart valves are presumably at a lower risk of perioperative thromboembolism, and warfarin therapy can reasonably be stopped in them two to three days preoperatively and restarted on the second postoperative day.

Complications of Anticoagulant Therapy

Hemorrhage

Epidemiology. Hemorrhage is the most common and important complication of anticoagulant therapy. The gastrointestinal and genitourinary tract systems and surgical wounds—including invasive radiologic procedures—are the most frequent sites of clinically significant hemorrhage. Bleeding may also occur from nasal, soft tissue, pulmonary, retroperitoneal, intracerebral, and other sources.[3-5,108,109] Excellent reviews of reported anticoagulant-induced bleeding complications are available.[109,110]

The frequency of major and minor episodes of hemorrhage differs considerably in published studies, in part because of inconsistent definitions of "major" and "minor" and varied study populations and methods.[108] Most studies have not reported the total time of exposure to anticoagulant therapy, so the annual incidence of hemorrhage cannot be calculated; the frequency of hemorrhage is instead reported as the proportion of study patients who bled during long-term anticoagulation. Table 4 lists these absolute rates of fatal, major, and minor hemorrhagic episodes for different thromboembolic disorders, as pooled from a number of studies.[111] More recently several groups have used life-table approaches to adjust for the varied durations of patient follow-up and to express the cumulative risk of hemorrhagic complications as a function of the duration of therapy.[3-5,28]

Table 5 summarizes the results of these investigations, along with the specific study populations and definitions used for major and minor hemorrhage. Because these studies primarily include patients already receiving long-term anticoagulation, but not all patients in whom therapy is started, they may underestimate the true risk of hemorrhage; patients bleeding early in the course of therapy would have been excluded from the studies.[108] The in-hospital period when long-term anticoagulant therapy is initiated in many patients carries a relatively high risk of hemorrhage. A recent investigation found that major and minor bleeding developed before hospital discharge in 5% and 6% of patients, respectively.[108]

Risk factors. There are few methodologically sound studies that adequately characterize independent risk factors for hemorrhage during long-term anticoagulation. Some putative risk factors are listed in Table 6.[112] More intense anticoagulation clearly increases the risk of hemorrhage. For initiating anticoagulant therapy in inpatients, PT ratios of 2.0 to 2.9 and greater than 3.0 increase the risk of major hemorrhage threefold and eightfold, respectively.[108] In patients anticoagulated for venous thromboembolism[19] and in those receiving anticoagulants for the first three months after bioprosthetic heart valve replacement,[20] low-intensity warfarin therapy is as effective as conventional warfarin therapy to a PT ratio of 1.5 to 2.0 and is associated with a 2.4-fold[20] to 4.0-fold[19] reduction in hemorrhagic complications. Still, 4% to 20% or more of major bleeding episodes and 30% to 90%

TABLE 4.—*Anticoagulant-Induced Hemorrhage in Various Thromboembolic Disorders (Pooled Rates)**

Thromboembolic Disorder	*Total Bleeding, %*	*Fatal Bleeding, %*	*Major Bleeding, %†*	*Minor Bleeding, %*
Ischemic cerebrovascular disease	28.7	4.8	7.0	21.8
Venous thromboembolism	22.6	0	8.1	14.4
Ischemic heart disease	19.1	1.0	4.7	10.5
Atrial fibrillation	15.2	0.003‡	0.01‡	14.2
Mechanical prosthetic heart valves	5.7	1.7	2.4	3.2

*Modified from Levine et al.[111]
†Resulting in admission to hospital, transfusion, or death (or all 3).
‡These rates may not be reliable estimates.

TABLE 5.—*Incidence of Warfarin-Related Hemorrhage by Life-Table Analyses*

			Incidence of Hemorrhage, by Type and Time					
			Major, %			*Minor, %*		
Source	*Study Population*	*Definitions of Hemorrhage*	*3 mo*	*12 mo*	*24 mo*	*3 mo*	*12 mo*	*24 mo*
Petitti et al, 1986[28]	370 HMO patients with venous thromboembolism	Major: resulting in admission to hospital or death; minor: not collated	10	18	26	NA	NA	NA
Gurwitz et al, 1988[4]	321 Patients in a university hospital anticoagulation clinic with various thromboembolic disorders	Major: requiring hospital admission, transfusion, or discontinuation of anticoagulation; minor: all other	3	6	12	14	23	30
Petty et al, 1988[5]	Same as Gurwitz et al[4]; 310 patients	Major: GI or CNS hemorrhage or death; minor: all other	1*	5	7	NA	NA	NA
Charney et al, 1988[3]	Same as Gurwitz et al[4]; 73 patients	Major: requiring hospital admission or discontinuation of therapy; minor: all other	0	0	0	25	49	61

CNS=central nervous system, GI=gastrointestinal, HMO=health maintenance organization, NA=not available

*At 6 months.

TABLE 6.—*Possible Risk Factors for Anticoagulant-Induced Hemorrhage**

- Intensity of anticoagulation
- Specific thromboembolic disorder requiring anticoagulation†
- Comorbid conditions
  - Severe anemia—hematocrit of less than 0.3 (30%)
  - Malignancy
  - Renal, hepatic, or cardiac dysfunction
  - Coagulopathy, especially thrombocytopenia
  - Recent operation or trauma
  - Gastrointestinal tract lesions
  - Severe, uncontrolled hypertension
  - Gait instability—risk of falls
- Concomitant drug therapy
  - Heparin, especially in patients older than 60
  - Aspirin
  - Nonsteroidal anti-inflammatory agents
  - Multiple drug therapy
- Poor patient compliance
- Inadequate physician supervision

*From Stults and Dere.[112]
†See Table 4.

of minor bleeding episodes occur with a PT ratio in the therapeutic range.*

Analytic reviews suggest that the risk of hemorrhage may vary with different thromboembolic disorders, being greatest in patients with ischemic cerebrovascular disease and venous thromboembolism (Table 4).[111] Some studies have not detected varying hemorrhagic risk with different thromboembolic disorders but also had a low statistical power to do so.[3,5]

Certain comorbid conditions may also increase the risk of hemorrhage. A multivariate discriminant analysis of in-hospital patients beginning anticoagulation found several independent risk conditions for major bleeding before discharge: the concurrent use of intravenous heparin in patients older than 60; severe anemia—hematocrit of less than 0.3 (30%); malignancy; serious cardiac illness—acute myocardial infarction, the use of intra-aortic balloon, or hypotension on admission; renal insufficiency—creatinine concentration 140 μmol per liter (1.6 mg per dl) or greater—or acute renal failure; and liver dysfunction—hyperbilirubinemia or macrocytosis of erythrocytes—and liver dysfunction that worsened during treatment.[108] A recent operation or trauma and coexisting malignant neoplasia appear to increase the risk of hemorrhage in patients anticoagulated for venous thromboembolism.[111,115] Uncontrolled hypertension may be a risk factor for cerebral bleeding in patients anticoagulated for ischemic cerebrovascular disease.[109,111] Thrombocytopenia and gait instability with its associated risk of falls are probably risk factors for anticoagulant-induced bleeding, although few data are available. Advanced age, by itself, does not appear to be a risk factor for oral anticoagulant-induced hemorrhage,[3-5,108,111,113] with the exception of patients older than 60 years who are concurrently receiving heparin therapy.[108]

A number of drugs potentiate or antagonize the effects of warfarin, either by altering its absorption, protein-binding, receptor-site affinity, or metabolism, by interfering with the production and absorption of vitamin K, or by affecting other hemostatic control mechanisms.[109,116] Drugs that regularly alter the effects of warfarin are listed in Table 7.[112] Drug potentiation of warfarin-induced hypocoagulability is estimated to contribute to 10% to 25% of bleeding episodes in anticoagulated patients.[117(pp491,492)] Even small doses of aspirin (500 to 1,000 mg per day) increase the rate of hemorrhage—primarily gastrointestinal—fourfold in patients taking warfarin.[59] The effect of other nonsteroidal anti-inflammatory agents on bleeding risk in anticoagulated patients is less well documented.[118] The use of phenylbutazone and piroxicam should definitely be avoided, as they prolong the prothrombin time in warfarin-treated patients.[118,119] Because all these agents can reversibly inhibit platelet function and cause direct gastrointestinal irritation, they should be used cautiously, if at all, in anticoagulated patients. When the administration of drugs known to alter the effects of warfarin must be initiated or discontinued, the warfarin dose should be adjusted by 25% to 30% in the appropriate direction with serial monitoring of the PT ratio every three to seven days for several weeks. The PT ratio should also be monitored more frequently when any other drug is added to or discontinued from a patient's regimen.

Poor medication compliance and inadequate physician supervision may result in excessive PT ratios and an increased risk of hemorrhage. Several North American and European studies have documented that 20% or more of patients receiving long-term anticoagulation have either inadequate or excessive PT ratios more than 50% of the time.[12,59,120,121] Thorough patient education and incorporation of patients into a regularly scheduled anticoagulation clinic with prompt telephone follow-up of missed appointments may facilitate monitoring and reduce complications.[3-5,109,122]

Warfarin Intoxication

The appropriate management of warfarin intoxication depends on the presence of or potential for life-threatening hemorrhage and the degree of prolongation of the prothrombin time.[123,124] Patients with no active bleeding and moderately excessive PT ratios (≤ 3.0 to 4.0) can be man-

TABLE 7.—*Drug Interactions With Warfarin*†*

Increases Warfarin Effect	*Decreases Warfarin Effect*
Allopurinol	Barbiturates
Anabolic steroids	Carbamazepine
Antiarrhythmics	Cholestyramine resin
Amiodarone	Estrogens
Quinidine	Griseofulvin
Antibiotics	Phenytoin
Cefamandole nafate	Rifampin
Cefoperazone sodium	Vitamin K (contained in some multiple vitamin and enteral nutrition products)
Ketoconazole	
Moxalactam disodium	
Neomycin sulfate	
Trimethoprim-sulfamethoxazole	
Cimetidine	
Clofibrate	
Disulfiram	
Phenylbutazone	
Piroxicam	
Sulfinpyrazone	
Sulfonylurea oral hypoglycemics	

*From Stults and Dere.[112]
†A large number of other drugs may also alter warfarin's effect on occasion.

*References 3, 5, 19, 20, 108, 111, 113, 114.

aged with the omission of one to three warfarin doses and observation. Patients with PT ratios of 3.0 to 4.0 or higher may additionally be given 2 to 4 mg of oral phytonadione (vitamin K_1), which will help reduce the excessive PT ratio within 24 to 48 hours; this dose of phytonadione will not make the patient refractory to subsequent warfarin therapy.[123] Patients with excessive PT ratios and bleeding that is not life-threatening or patients with anticipated hemorrhage from a scheduled surgical procedure should receive phytonadione, 5 to 10 mg, subcutaneously. This dose will reduce the PT ratio within 6 to 12 hours in most patients without making them refractory to subsequent warfarin therapy.[123] Because warfarin has a longer half-life than phytonadione, the PT ratio may rise again within 24 hours, requiring the readministration of phytonadione.[125] Patients with active, life-threatening hemorrhage require the immediate administration of intravenous clotting factors, either fresh frozen plasma or, if large volumes of fluid are contraindicated, prothrombin complex concentrates; subcutaneous phytonadione should also be given. Intravenous phytonadione may have a procoagulant effect within three to four hours in patients with normal hepatic function,[124] but more than 40 cases of severe, anaphylactoid reactions, with several fatalities, have been reported with its use.[109] Protocols for the cautious administration of intravenous phytonadione have been proposed, primarily for use in patients with central nervous system or life-threatening gastrointestinal bleeding.[124]

Diagnostic Evaluation of Anticoagulant-Induced Hemorrhage

Limited data are available concerning the appropriate extent of a diagnostic evaluation of gastrointestinal and genitourinary tract bleeding in anticoagulated patients. Whether the evaluation should vary according to the site of bleeding (gastrointestinal versus genitourinary), magnitude of bleeding (gross versus microscopic), or degree of prothrombin time ratio prolongation (excessive versus therapeutic) has not been completely determined. Table 8 summarizes the results of several studies.[126-132] The proportions of patients with organic lesions and neoplasms may be underestimated in some of these studies, since not all patients underwent all appropriate diagnostic tests, especially endoscopic procedures. Based on the considerable yield of diagnostic investigation in these studies, essentially all gastrointestinal bleeding, whether from the upper or lower gastrointestinal tracts, gross or microscopic, and irrespective of a patient's PT ratio, should be thoroughly evaluated. Patients with lower gastrointestinal tract bleeding who are excessively anticoagulated are less likely to have a specific organic lesion identified; their initial evaluation may consist of sigmoidoscopy and double contrast barium enema, with colonoscopy reserved for those who have recurrent bleeding with a therapeutic PT ratio.[126] A thorough diagnostic evaluation with at least intravenous pyelography and cystoscopy should also be carried out in patients with gross or microscopic genitourinary tract bleeding and a therapeutic PT ratio. There are few data available concerning the significance of gross or microscopic genitourinary bleeding in excessively anticoagulated patients. Pending further studies, these patients should at least be closely followed with a complete evaluation if hematuria persists or recurs during therapeutic anticoagulation.

Nonhemorrhagic Complications of Anticoagulants

Warfarin. Warfarin therapy has been associated with four dermatologic lesions: ecchymosis and purpura from excessive anticoagulation; maculopapular, vesicular, and urticarial reactions caused by drug allergy; hemorrhagic skin necrosis; and the "purple toes" syndrome.[14,133] The first of these complications can be limited by carefully regulating the intensity of anticoagulation. Patients manifesting cutaneous warfarin allergy can generally be switched without cross-reaction to the coumarin congener, dicumarol.[133]

Warfarin-induced hemorrhagic skin necrosis is a rare complication—reported world experience of about 200 cases—characterized pathologically by occlusion of cutaneous capillaries and venules and subcutaneous veins.[14,109] About 85% of cases appear in the first ten days of therapy,

TABLE 8.—*Results of Diagnostic Evaluation of Anticoagulant-Induced Hemorrhage*

Source	Patients Evaluated, No.	Bleeding Site	Magnitude of Bleeding	Prothrombin Time (PT) Ratio Range	% Patients With Organic Lesions/ % Patients With Neoplasia	Comment
Wilcox and Truss, 1988[126]	50	Upper GI tract	Gross	Variable	80/3	High yield of lesions—mostly acid peptic disorder at all PT ratios
		Lower GI tract	Gross and occult	Variable	52/30	Low yield of lesions with excessive PT ratio
Jaffin et al, 1987[127]	16	Pan-GI	Occult	Therapeutic*	75/25	Hemoccult positivity not related to degree of anticoagulation
Kewenter et al, 1984[128]	128	Only lower GI tract evaluated	Occult†	Variable	25/23	Hemoccult positivity not related to degree of anticoagulation
Antolak and Mellinger, 1969[129]	17	GU tract	Microscopic (11 patients)	Therapeutic*	82/18	
			Gross (6 patients)		83/33	
Schuster and Lewis, 1987[130]	29	GU tract	Microscopic (5 patients)	Therapeutic	20/0	Four patients with gross hematuria caused by organic lesions had previous microscopic hematuria
			Gross (24 patients)		67/17	
Cuttino et al, 1987[131]	24	GU tract	Gross	Therapeutic	50/20	Only 50% of patients had cystoscopy
Barkin et al, 1983[132]	17	GU tract	Gross	Therapeutic	17/12	

GI=gastrointestinal, GU=genitourinary

*Except one patient.
†Rehydrated guaiac slides.

presenting as a discrete, erythematous, maculopapular, and painful eruption with a predilection for areas of abundant adipose tissue—buttocks, breasts, anterior thighs, and abdominal wall; 25% to 40% of cases have multiple lesions, and 20% of these are bilaterally symmetric.[14] Between 75% and 90% of cases occur in women, presumably because of their more prominent adipose tissue.[109] These lesions may progress and become hemorrhagic, bullous, and necrotic and may require skin grafting or result in limb amputation or even death. The pathophysiology of this complication is poorly understood but may relate in part to a transient hypercoagulable state induced by an early depletion of anticoagulant proteins, such as protein C, before the suppression of procoagulants; some patients prove to have absolute or functional protein C deficiency, while others have had malignant neoplasia.[109,134] Treatment consists of the cessation of warfarin, local wound care, and, possibly, administering phytonadione or heparin or both.[14,109] During the first two weeks of warfarin therapy, patients should be advised to frequently examine at-risk areas for evidence of erythema and tenderness and report these immediately to their physician.

The "purple toes" syndrome, another rare complication that can be associated with the use of warfarin, usually occurs in the first two months of therapy in elderly patients with extensive aortic atherosclerotic disease.[135] (This syndrome may also occur unrelated to anticoagulant therapy.[136]) Bilateral, painful, purplish discoloration develops in the plantar and lateral sides of the toes, which fades with local pressure or elevation and waxes and wanes with time. The lesions appear to be caused by cholesterol microembolization from ulcerated, atherosclerotic plaques in the aorta and other large arteries.[135] Early recognition of the syndrome and the cessation of warfarin therapy are important because progressive cholesterol embolization can involve the renal and cerebral circulations and result in renal failure, stroke, and death.[135]

Finally, rare cases of cholestatic hepatic injury due to warfarin therapy have been described.[109,137]

Heparin. Nonhemorrhagic complications associated with heparin therapy[109] include thrombocytopenia,[138] osteoporosis,[94,99,100] hyperkalemia,[139] elevated values on liver function tests,[140,141] and a variety of cutaneous lesions.[142,143] The incidence of these complications in outpatients treated with adjusted-dose subcutaneous heparin is unknown, although probably low. Heparin-induced thrombocytopenia has been described both with full and low doses administered intravenously or subcutaneously and usually develops within the first 15 days of therapy[138]; whether it can develop after this period is unknown. The thrombocytopenia occurs more commonly with the use of bovine lung heparin than with intestinal heparin and is usually mild, asymptomatic, and transient but in rare cases can be severe and associated with hemorrhage or arterial thromboembolism.[138] The value of regular screening for thrombocytopenia beyond the first two weeks of therapy has not been documented, and firm guidelines cannot be proposed at this time.

Heparin-induced osteoporosis was previously discussed. A careful review of the benefit:risk ratio related to this complication is necessary before using adjusted-dose subcutaneous heparin for longer than six months.

Both full- and low-dose heparin therapy can suppress adrenal aldosterone production.[144] This effect can result in clinically significant hyperkalemia in certain patients with renal disease and hyporeninemia, especially those with diabetes mellitus.[139] Using heparin can also result in mild transient, reversible increases in serum aminotransferase and γ-glutamyl transpeptidase levels, presumably due to subcellular hepatic damage.[140,141]

Cutaneous lesions resulting from subcutaneous heparin include local ecchymosis and hematoma, urticarial-type reactions, large indurated and erythematous plaques, and, rarely, skin necrosis similar to that induced by warfarin.[142,143] These last three lesions may occur at sites at a distance from the injection site.

Administering Anticoagulants

Warfarin Therapy Initiation

Because of its complex pharmacokinetics and pharmacodynamics, warfarin is a difficult drug to dose. In the general population there is a 10-fold to 20-fold variation in the required maintenance dose, which cannot be adequately predicted before beginning therapy.[145,146] As a result, during the induction phase of therapy, overanticoagulation and an excessive time to reach a therapeutic PT ratio are common occurrences.[147] Various methods have been proposed to assist clinicians in predicting the eventual maintenance dose of warfarin.[146-151] These methods are based on empiric data concerning the prothrombin time response to the first several doses of warfarin[148] or pharmacokinetic and pharmacodynamic indices estimated from population studies.[147,150,151] Unfortunately, all of these methods have substantial limitations. Some require computer software programs[147] or laboratory measurements[151]—warfarin plasma concentrations or factor VII activity levels—not immediately available to most clinicians. Most have not been shown to be superior to the usual empiric approach to warfarin dose adjustment by skilled clinicians.[146,152] Still, clinicians less experienced with empiric warfarin dosing may benefit from using these programs.[147]

Several considerations may assist clinicians in the empiric approach to warfarin dosing. Because its maximal antithrombotic effect does not occur until four to seven days after the initiation of therapy, warfarin therapy should be overlapped with therapeutic doses of heparin for at least this period of time when treating patients with acute thromboembolism.[13] This overlap period may theoretically also help prevent the rare cases of warfarin-induced skin necrosis. Although there are no published studies of other thromboembolic disorders, for patients with venous thromboembolism, the early initiation of a warfarin regimen within one to two days of starting a seven- to ten-day course of heparin is safe, cost-effective, and can significantly shorten the length of hospital stay.[153,154] When the activated partial thromboplastin time is within 1.5 to 2.0 times control, the use of heparin directly prolongs the prothrombin time by only one to two seconds in most patients; about 20% of patients, however, may have a three- to five-second prolongation of the prothrombin time.[155] Because of this unpredictable change, the PT ratio should be redetermined shortly after heparin therapy is discontinued. Additionally, when a low-intensity warfarin regimen is desired, a PT ratio of 1.5 to 1.6 should be obtained during concurrent heparin therapy in anticipation of a possible decrease in the ratio to 1.3 to 1.4 when heparin therapy is discontinued.

Large loading doses of warfarin—greater than 15 mg per day—should be avoided because they do not hasten the onset of an antithrombotic effect but may increase the bleeding

risk.[156] Some clinicians initiate warfarin therapy with a dose of 10 mg per day for three days and estimate the maintenance dose of warfarin according to a variety of prediction equations that use the PT ratio measured on the fourth day.[157] Using this fixed loading dose regimen, however, by the fourth day of warfarin administration, a third of patients are excessively anticoagulated but another third are insufficiently so.[148,157,158] Other clinicians, therefore, prefer to give an initial 10-mg dose and measure the PT ratio daily, with the second and third doses adjusted according to the PT ratio responses to previous doses; a maintenance dose may then be estimated according to the measured PT ratio on day 4.[148] With the use of either method, clinicians must be aware of patients who are particularly sensitive to warfarin and whose PT ratios increase to 1.3 to 1.5 in the first 24 to 48 hours of therapy; such patients usually require maintenance doses of less than 5 mg a day.[159] In contrast, patients with no change in their PT ratio after three 10-mg-a-day doses are relatively resistant to warfarin and usually require maintenance doses of 7.5 to 10.0 mg or higher per day.[159]

The average maintenance doses for conventional and low-intensity warfarin regimens are 5 to 6 mg a day and 4 to 5 mg a day, respectively,[19,20] although, as previously noted, there is tremendous variation. Elderly patients may, on average, require slightly lower maintenance doses.[160-162] Once the PT ratio is in the desired range for three successive days, it may be measured two to three times in the subsequent week, then weekly for two to three weeks, and, if stable, on a monthly basis thereafter for most patients. At least ten days, and a longer period of time in some patients, is required to reach a steady-state anticoagulant response to a given maintenance dose of warfarin.[157]

Warfarin is available in several tablet sizes—2, 2.5, 5, 7.5, and 10 mg. To minimize errors, only a single brand and tablet size should be prescribed; scored 5-mg and 2-mg tablets are useful in many patients for conventional and low-intensity warfarin therapy, respectively. To receive an appropriate maintenance dose, many patients will need to alternate doses—for instance, 5.0 mg alternating with 7.5 mg or 5.0 mg for two days and 7.5 mg every third day. To decrease errors, these patients should use a calendar with each day's dose prerecorded.

Long-term Follow-up of Warfarin Therapy

Several groups have suggested that to satisfactorily balance the risks of thrombosis and hemorrhage, the prothrombin time ratio should be maintained within the desired therapeutic range for at least 70% of the time.[120,163,164] In patients with a record of good anticoagulant control, many clinicians arbitrarily monitor the PT ratio at monthly intervals.[157,165] Selected patients whose monthly PT ratio measurements have been consistently stable may have the monitoring interval gradually extended to 6 to 12 weeks without a significant loss of control.[166,167] In contrast, other patients may require monitoring more frequently than on a monthly basis to maintain satisfactory levels of anticoagulation.[120,121]

During long-term follow-up, PT ratios may fall outside the desired therapeutic range due to one or more causes:

- Inaccurate laboratory measurement;
- Poor patient compliance—medication error or missed dose;
- Inappropriate dosing by the physician prescribing warfarin;
- Drug interactions (see Table 7);
- Sustained major alterations in dietary vitamin K (see Table 9)[112,168];
- Concurrent illness—such as biventricular congestive heart failure—affecting liver function;
- Use of a different brand formulation of warfarin in the same patient[169] (three brand formulations are currently available in the United States: Coumadin [Du Pont], Panwarfin [Abbott], and Sofarin [Lemmon]);
- Otherwise unexplained alterations in warfarin pharmacology.[152]

Prothrombin time ratios significantly outside the desired range should be promptly repeated to rule out laboratory error; for high PT ratios, patients should also withhold warfarin pending the second test results. If the second PT ratio is similarly out of range, the possible causes as listed should be investigated and the dose of warfarin adjusted appropriately, with the PT ratio remeasured within two to seven days, according to the circumstances. As noted previously, some patients with high PT ratios may require judicious vitamin K administration. For PT ratios close to the desired range, dosage changes for undesirable trends should generally not exceed 10% to 15% so as to avoid wide fluctuations in the ratios.[165]

Anticoagulation clinics can facilitate more efficient outpatient anticoagulant therapy and may possibly reduce the frequency of complications.[3-5,109,170,171] Such clinics may be hospital-based with patient referrals from primary care physicians and staffed by a trained registered nurse or physician's assistant with appropriate supervision from a physician expe-

TABLE 9.—*Patient Education for Outpatient Anticoagulation**

Symptoms and signs
Bleeding—including retroperitoneal
Recurrent thromboembolism
Skin necrosis and purple toe syndrome in warfarin-treated patients
Measures to prevent bleeding complications
Avoid aspirin; use acetaminophen for mild analgesia
Avoid prescription or over-the-counter medications without previously notifying physician
Avoid alcohol or limit its use to 3 oz per day
Minimize injury: avoid contact sports, climbing, and power tools; use electric razor for shaving and a soft toothbrush; bathtub safety with floor mats and grab-bars; use gloves when gardening; wear shoes at all times
Avoid major increases in vitamin K consumption in warfarin-treated patients
Vitamin-nutrient supplements containing vitamin K
Continuous daily intake of green tea, broccoli, cauliflower, brussels sprouts
Administration and monitoring of anticoagulant therapy
Maintain calendar of warfarin doses
Take warfarin at same time daily, preferably in the evening
Notify physician of all missed or improper doses
Avoid extra doses to compensate for missed doses
Have prothrombin time (PT) ratio checked at least monthly unless otherwise directed by physician; contact physician for results of all PT ratio measurements within 24 hours
Keep address and telephone number current with physician
Carry Medic Alert bracelet, necklace, or wallet card at all times
Notify other physicians and dentists of anticoagulant therapy
Advise fertile women of teratogenic risk of warfarin
Contact physician immediately if menses delayed more than 2 to 3 days
Advise heparin-treated patients of osteoporosis risk

*From Stults and Dere.[112]

rienced with long-term anticoagulation. Alternatively, within a single practice, all anticoagulated patients may be scheduled on a given day(s) each month to see the office nurse or to have a PT ratio measurement. At scheduled visits, the clinic professional measures the PT ratio, seeks adverse reactions and complications, and reinforces patient education. A hematocrit, urine dipstick for heme, and stool guaiac tests may also be done at specified intervals—such as every six months—to screen for occult bleeding. Patients can be informed of the PT ratio and any necessary dose changes within 24 hours. All test results and drug doses are recorded on flow sheets. This will facilitate regular quality control because the clinician can regularly monitor the proportion of PT ratios within the therapeutic range both longitudinally in individual patients and cross-sectionally within the anticoagulation clinic.[120,163,171] Patients missing their appointments may be promptly contacted by phone or letter, making it more difficult for them to be lost to follow-up within a busy practice.

Although not rigorously shown to reduce the frequency of complications,[122] thorough oral and written instructions should be provided to patients and periodic reviews done of patients' understanding of this information. Table 9 lists important concepts to transmit to patients.

Adjusted-Dose Subcutaneous Heparin

For long-term outpatient anticoagulation, adjusted-dose subcutaneous heparin is generally administered every 12 hours[17]—every 8 hours by some clinicians[172]—in a dose sufficient to prolong the mid-interval activated PTT to 1.5 to 2.0 times control. The maximal response of the activated PTT occurs four to six hours after subcutaneous administration, and a sustained anticoagulant effect persists throughout the injection period.[17] Long-term prophylactic therapy may be initiated with a dose of 7,500 to 10,000 units every 12 hours and titrated daily for three to four days until the desired activated PTT is reached. (Note that this dosing regimen is insufficient when subcutaneous heparin is to be substituted for intravenous heparin in the *initial* treatment of acute venous thromboembolism.[173-175]) In patients who are completing a course of therapeutic (activated PTT 1.5 to 2.0 times control) intravenous heparin, an initial estimate of the subcutaneous dose to be administered every 12 hours is about a third the total 24-hour dose of intravenous heparin. In one study, the mean required dose for long-term outpatient anticoagulation of patients with venous thromboembolism was 10,000 units every 12 hours.[17] For nonpregnant patients, the required dose of heparin appears to be stable over time, and subsequent monitoring of the activated PTT may not be necessary.[17] Pregnant patients, however, have progressively increasing heparin requirements up until delivery and should be monitored at least monthly and more frequently in the third trimester.[12,172] Heparin requirements decrease considerably in the immediate postpartum period.[93] The heparin is administered with a deep, subcutaneous, intrafat injection with rotation of sites over the entire abdominal wall, remaining 5 cm (2 in) or more away from the umbilicus. Injections should be avoided in the arms and legs, where absorption may be more erratic. The patient grasps a 2.5- to 5-cm (1- to 2-in) layer of fat between the fingers, holds it away from the deeper tissues, injects with a 25- or 26-gauge (1/2- or 5/8-in) needle attached to an insulin or tuberculin syringe, and applies pressure (not massage) to the site for 30 seconds.[176] Sodium heparin at a concentration of 20,000 or 40,000 units per ml, or calcium heparin at a concentration of 25,000 units per ml, is most convenient. Although calcium heparin may have a more prompt anticoagulant effect,[174] this is probably of little importance in long-term outpatient anticoagulation. Porcine intestinal sources of heparin may be preferred over bovine lung sources owing to a lower incidence of thrombocytopenia.[138]

Addendum

Since this article was accepted for publication, Landefeld and Goldman in a study of 187 patients starting outpatient therapy with warfarin identified five independent risk factors for major bleeding:

- Age older than 65 years;
- History of stroke;
- History of gastrointestinal bleeding;
- Comorbid conditions of recent myocardial infarction, renal insufficiency, or severe anemia; and
- Atrial fibrillation.

They were able to predict the cumulative incidence of major bleeding at 48 months from 2% in low-risk patients to 63% in high-risk patients.[177]

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Medical Progress

Cardiovascular Effects of Alcohol

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The effects of alcohol on the heart include modification of the risk of coronary artery disease, the development of alcoholic cardiomyopathy, exacerbation of conduction disorders, atrial and ventricular dysrhythmias, and an increased risk of hypertension, hemorrhagic stroke, infectious endocarditis, and fetal heart abnormalities.

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Although the harmful effects of alcohol on the heart were first reported more than a century ago, only in the past 30 years have investigators clarified the effects of the consumption of alcohol on the cardiovascular system through studies of animals and humans.[1,2]

Alcohol can exacerbate hypertension and affect levels of other indicators of risk for coronary artery disease (CAD) and stroke. These changes place heavy drinkers at a greater risk for a myocardial infarction, sudden cardiac death, and stroke. Considerable controversy persists, however, regarding the possible advantages of light alcohol consumption, usually defined as less than 1 oz (two drinks) per day.

In this essay I review recent evidence regarding the harmful and potentially beneficial effects of alcohol use on the human heart. The initial and long-term responses of the myocardium to alcohol use will be considered first, along with its treatment and possible reversibility. I will then describe the effects on cardiac conduction and rhythm, noting the increased risk of sudden cardiac death in heavy drinkers. I discuss the effects of alcohol intake on hypertension and other risk indicators for coronary artery disease and summarize the epidemiologic evidence linking alcohol use to myocardial infarction and stroke. Finally, I describe the relationships of alcohol use to infectious endocarditis and fetal heart abnormalities.

Investigational Issues

Studies of the alcohol-heart relationship are methodologically difficult for many reasons. One major issue involves comparisons of nondrinkers and drinkers; the two groups are rarely formed randomly. Self-reporting of current and past drinking habits is usually obtained from those who choose to participate in a study, leading to certain problems.

Included among nondrinkers (current abstainers) are both ex-drinkers and persons who never drink; the former may have cardiac problems or altered cardiovascular risk factors due to their previous excessive consumption. In a prospective study of 7,735 British men, investigators found that long-term ex-drinkers had many characteristics that increase their cardiovascular risk. They were more likely to be unmarried and to work in manual occupations. Their prevalence of cigarette smoking, hypertension, and obesity was much higher than that of persons who never drink but was similar to that of moderate and heavy drinkers. Of all groups, ex-drinkers had the highest prevalence of angina and definite myocardial infarction by electrocardiogram, and they had a rate of recall of ischemic heart disease diagnosed by their physician that was twice that of drinkers.[3] Lifelong abstainers have less psychosocial dysfunction than ex-drinkers, are more likely to be religious, have less education, live in rural areas, and have lower incomes.[4,5] Thus, ex-drinkers clearly should be separated from the never-drinking group.

Another methodologic obstacle is defining the drinking population. In most population studies, those who do not participate have different characteristics from those who do. For example, in establishing the Göteborg (Sweden) Primary Prevention Trial study population, 25% of 10,000 invited men declined to be enrolled. After a 12-year follow-up, investigators found that nonparticipants had twice the mortality as participants; most of the excess deaths were sudden. Nonparticipants were more often registered with the Board of Social Welfare for social problems and alcohol abuse.[6]

Those who do participate may not report alcohol intake accurately,[7] although one study of patients and spouses showed agreement within one category of consumption in 90% of cases.[8] If reporting is accurate, then the decision of how to aggregate the data obtained must be made. Are seven drinks every Saturday night equivalent to one drink daily each week in terms of health effects? Many investigators express alcohol consumption in terms of ounces of pure ethanol consumed per day or week.[9] One drink can be defined as a 12-oz beer with 3% to 5% ethanol, a 5-oz glass of wine (12%), or a 1.5-oz shot of spirits (80 proof = 40%). Each contains 0.6 oz (17 ml = 13.6 grams) of ethanol.

Myocardial Dysfunction

Pathophysiology

Animal models are traditionally used to elucidate the pathophysiology of human diseases, but this is difficult with alcoholic cardiomyopathy. Myocardial changes consistent with subclinical human heart disease have been produced, but impairment leading to congestive heart failure has not been replicated.[1]

Several mechanisms have been postulated by which eth-

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ABBREVIATIONS USED IN TEXT

BP = blood pressure
CAD = coronary artery disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein
LV = left ventricular
VLDL = very-low-density lipoprotein

anol damages the heart. These include a direct toxic effect, action by ethanol metabolites, and a neurohumoral mechanism.[1] Mitochondrial changes—enlargement, decreased respiration, release of enzymes, and reduced ion transport—have been observed after long-term exposure to ethanol, associated with membrane damage, increased calcium flux, impaired adenosine triphosphatase activity, decreased fatty acid oxidation, and depressed adenosine triphosphate levels.[10-12] Persistent impairment of mitochondrial function may be due to the formation of fatty acid ethyl esters, which bind to mitochondria. When the esters are hydrolyzed, free fatty acids are released, leading to the uncoupling of oxidative phosphorylation.[13]

Some investigators think that acetaldehyde mediates this damage.[14] The effects of ethanol's major metabolites, acetaldehyde and acetate, have also been investigated in the peripheral and cerebrovascular circulations. The vasoconstrictor and vasodilator effects of these metabolites may be related to calcium movement across vascular smooth muscle cell membranes.[15]

Interstitial edema and focal areas of necrosis are noted histologically in myocardial tissue. Coronary arteries are usually patent, but it should be remembered that studies often exclude subjects with symptomatic coronary artery disease.

It is difficult clinically to distinguish alcohol-induced myocardial damage from other types of dilated cardiomyopathy,[2] so often the diagnosis must be made by excluding other causes in a person with a history of heavy alcohol intake.

Epidemiology

A disproportionate number of cases of alcoholic cardiomyopathy occur in men, even when sex differences in alcohol intake are considered. Similarly, preclinical cardiomyopathy is detected in men more frequently than in women.[16] Precise prevalence and incidence figures have yet to be determined, largely because of the methodologic difficulties discussed previously. The typical symptomatic patient is a middle-aged man who has been a heavy drinker for at least ten years, deriving 30% to 50% of his calories from alcohol. It is suspected, however, that most persons with alcoholism have subclinical heart disease. An autopsy study in Detroit of alcoholic persons with no premortem clinical signs of cardiomyopathy revealed an increased heart size in many cases; in those hearts without cardiomegaly, gross and microscopic pathologic changes consistent with cardiomyopathy were noted.[17]

In several cities, the addition of cobalt to the beer-brewing process resulted in a toxic cardiomyopathy distinct from the effect of alcohol on the myocardium.

Nutrition

For some years, the pathogenesis of alcoholic cardiomyopathy was attributed to nutritional deficiencies such as beriberi because both conditions may result in congestive heart failure. In contrast to alcoholic cardiomyopathy, however, beriberi is characterized by a high cardiac output due to peripheral arteriolar dilation. Chest pain is nonspecific, and the electrocardiogram may be normal.[18] Thiamine deficiency in this condition may result from inadequate dietary intake or through increased metabolism. The latter is particularly the case in beer and wine drinkers, perhaps because the higher carbohydrate content of those beverages can increase thiamine requirements. Fortunately, cardiac sequelae can be reversed with the administration of thiamine.[19]

Other nutritional deficiencies may arise if calories from alcohol replace those from other sources. This occurs more often in alcoholic persons than in mild to moderate drinkers. Alcohol interferes with food absorption and may alter appetite and satiety.[20]

Compared with nondrinkers, Scottish men with moderate alcohol intake had lower intakes of total, saturated, and monounsaturated fats. Persons drinking one drink per day or less had a higher intake of fiber and polyunsaturated fatty acids.[21] These differences may play some role in the relationship of alcohol intake to the coronary artery disease incidence, as will be described.

Initial Myocardial Effects

Readers will recall that the cardiac output is the product of heart rate and stroke volume and that the product of the cardiac output and total peripheral resistance equals the mean arterial blood pressure. The stroke volume often reflects the myocardial contractile state, but the dynamic relationships among these variables require consideration of each during an intervention.

The initial effects of alcohol ingestion are highly dose dependent. After only 2 oz of whisky, the cardiac output and stroke volume increased in normal subjects, while the same measures decreased in cardiac patients.[22] The enhanced hemodynamics in normal subjects reflect increased circulating catecholamines, which in turn can increase contractility. When this sympathetic nervous system response is blocked pharmacologically, the myocardial depressant effect of acute ethanol ingestion becomes clear.[23]

At higher doses, peripheral vasodilation is noted, along with a decrease in blood pressure and compensatory increases in heart rate.[24] During isometric[25] or dynamic exercise,[26] these hemodynamic changes compensate for the myocardial depressant effect of alcohol. Alcohol may potentiate the effects of pharmacologic vasodilators such as nitroglycerin.[27]

In patients with moderate to severe congestive heart failure—New York Heart Association classification III and IV—no decrease in myocardial performance was noted after 0.9 grams per kg body weight of vodka was consumed, reflecting the vasodilatory properties of alcohol.[28] When patients with transmural myocardial infarction were given 2 oz whiskey seven to ten days after their infarction, however, the stroke volume and cardiac output both decreased due to a decline in left ventricular contractility in the peri-infarct zones.[29]

Moreyra and co-workers reported three cases of acute myocardial infarction in young persons after an episode of heavy alcohol intake. All had normal coronary arteries, suggesting that thromboembolism or coronary artery spasm might have been involved.[30]

Long-term Myocardial Effects

Long-term damage to the myocardium in drinkers is related to both the frequency and duration of excess alcohol consumption. Earlier studies examined the cardiothoracic ratio on chest roentgenograms and noted sinus tachycardia and T-wave abnormalities on electrocardiograms, but both findings were nonspecific.[31] Several authors have described pronounced T-wave abnormalities in patients with alcoholic cardiomyopathy who had hypomagnesemia.[32]

Using systolic time intervals derived from phonocardiography and electrocardiography, investigators noted significant differences in the mean values of the pre-ejection period and left ventricular ejection time between normal subjects and asymptomatic alcoholic persons, but considerable overlap remained between values in the two groups.[33] Newer noninvasive cardiovascular diagnostic techniques, however, have successfully differentiated asymptomatic drinkers with early myocardial changes from normal healthy persons.

Echocardiographic studies in persons recovering from alcoholism have been carried out during the first week,[31] at least two weeks after,[33] and an average of a month after[34] their last alcoholic drink. Using values greater than two standard deviations above the mean as abnormally high, Askanas and colleagues noted that half of their asymptomatic alcoholic subjects (three to six days after last drink) had abnormally increased thickness of the intraventricular septum and posterior left ventricular (LV) wall, leading to an abnormally high estimate of LV mass. Echocardiographic indices of contractility (percent fractional shortening, ejection fraction, and circumferential fiber shortening) and chamber diameters (left atrial and left ventricular at end-diastole and end-systole) were much less specific.[31]

Mathews and associates studied 22 asymptomatic and 11 symptomatic alcoholic persons at least 14 days after their last drink. They also found about half of their asymptomatic subjects had abnormally high septal and free wall LV thicknesses and LV mass. Among their symptomatic patients, all 11 had abnormally high left ventricular dimensions and 10 of the 11 had elevated left ventricular mass. In the latter group, however, septal and wall thicknesses were only modestly increased, compatible with a dilated cardiomyopathy without hypertrophic thickening of the myocardium.[33]

Kino and co-workers examined 145 alcoholic men in Japan, noting increased echocardiographic estimates of left ventricular mass with consumption exceeding 125 ml of ethanol daily for ten years or more.[34] Their studies were done over a wide range of abstention times (minimum one week, average one month), however, raising the issue of a possible regression of LV changes after the cessation of alcohol intake.[34] In fact, an improvement in myocardial function after several months of abstention has been found using echocardiography[35,36] and radionuclide ventriculography.[37]

Cardiac catheterization can document reduced cardiac output and elevated filling pressures. Contrast ventriculography often reveals an enlarged, hypocontractile left ventricle, but a tendency for a preservation of contractility in the basal portions has been noted.[2]

Clinical Course and Treatment

Several authors described the natural history of alcoholic cardiomyopathy in the decades before the availability of vasodilators and other pharmacologic agents for the treatment of dilated cardiomyopathies. Tulane University (New Orleans) investigators used prolonged bed rest (6 to 671 days) but concluded that the ultimate prognosis was poor because of their subjects' unwillingness to accept the immobility and to resist the temptation to resume drinking.[38] Demakis and associates observed a strong relationship between abstaining and an improved clinical state in patients without prolonged bed rest. Among abstaining patients, 61% showed clinical improvement, compared with only 10% of heavy drinkers.[39]

The symptoms and signs of alcoholic cardiomyopathy are consistent with the extent of congestive heart failure. Frequently reported are orthopnea, paroxysmal nocturnal dyspnea, and dyspnea on exertion. Physical signs include a sinus tachycardia, third and fourth heart sounds, rales, hepatomegaly, and peripheral edema. The results of cardiac catheterization studies in such patients confirm increased left ventricular end-diastolic (filling) pressures, leading to increased pulmonary vascular pressures and the symptoms of congestive heart failure.

The most important goal of treatment is to help a patient remain abstinent, with the hope of reversing the myocardial changes. Most quantitative studies suggest that this process may require as long as a year or more,[37,40,41] although cases of quicker recovery have been reported.[35]

In general, the pharmacologic therapy for alcohol-induced myocardial dysfunction follows current recommendations for dilated cardiomyopathy of any cause.[42,43] In the presence of a dilated left ventricle, administering vasodilators and digoxin is indicated, as well as the use of diuretics when an increased LV filling pressure has resulted in symptoms of congestion. Angiotensin-converting enzyme inhibitors are also useful; when combined with the use of diuretics, they minimize the probability of hypokalemia.[42] Alderman and Coltart point out that digoxin should be used cautiously because of an increased susceptibility to toxicity in patients with advanced heart failure and because hypokalemia is more common in heavy drinkers. They also recommend caution in anticoagulating such patients; the possible benefit of such treatment to reduce the likelihood of emboli may be counterbalanced by hepatic dysfunction and less reliability of such persons in self-administering medication.[2]

Because left ventricular failure is frequently accompanied by dysrhythmias and conduction disorders, these will now be considered in the context of alcoholic cardiomyopathy.

Conduction Disorders and Dysrhythmias

Studies in animals and humans have documented various conduction disorders in chronic alcoholism, including a prolonged PR interval, Mobitz I and II block, right and left bundle branch block, and complete heart block.[44-46] In one study, the ingestion of 60 ml of whiskey prolonged atrial conduction and decreased ventricular refractory periods in nonalcoholic cardiac patients.[22]

More common are atrial and ventricular dysrhythmias, the prevalence of which depends on the frequency and duration of alcohol intake and the underlying state of the myocardium.

Atrial Dysrhythmias

Various atrial dysrhythmias have been noted after spree or holiday drinking, including premature atrial contractions, atrial tachycardia, atrial flutter, and atrial fibrillation.[45]

Suspecting that alcohol use was part of the cause of new cases of atrial fibrillation, Lowenstein and co-workers reviewed the records of 40 such consecutive patients in their hospital. They found that alcohol intake had caused or contributed to the dysrhythmia in 35% of all cases and in 63% of persons younger than 65 years.[47] Case-control studies of this phenomenon have documented an association with alcohol use in 15% to 63% of cases of paroxysmal atrial fibrillation.[48,49] Infrequent drinkers may also have atrial fibrillation after a drinking binge.[50] Electrophysiologists have induced atrial fibrillation in susceptible patients with as little as 60 ml of whiskey.[51] In one case, atrial fibrillation recurred in a man who used large amounts of alcohol-rich breath spray.[52] Investigators have suggested the involvement of several mechanisms, including increased levels of circulating catecholamines and altered myocardial refractory periods and conduction times.[51,53,54]

The question may next be asked if habitual alcohol users are more susceptible to these conditions. One group found no differences in the prevalence of atrial dysrhythmias between normal subjects and heavy drinkers with normal myocardial function.[55] In another study, information about heavy drinkers with presumed greater myocardial involvement was obtained when 1,322 persons reporting consuming six or more drinks per day were compared with 2,644 drinkers who reported drinking at least monthly but less than daily. The relative risk in the heavier drinkers was at least doubled for atrial fibrillation, atrial flutter, supraventricular tachycardia, and atrial premature complexes.[56]

Ventricular Dysrhythmias

Increased ventricular ectopic activity, including ventricular tachycardia, has been documented after intensified ingestion of alcohol in persons with[53] and without[57,58] apparent heart disease. In addition to catecholamine effects, possible etiologic factors include heterogeneous refractory periods throughout the myocardium and prolonged His-Purkinje intervals.[53]

Ventricular dysrhythmias may also occur in the alcohol withdrawal period, although certainty about their cause is complicated by the presence of coronary artery disease,[59] electrolyte and mineral disorders,[60] delirium tremens,[61] and medical treatment.[62,63]

Sudden Cardiac Death

Although ventricular dysrhythmias are more common—and more easily induced—in heavy drinkers, evidence for a notably increased risk of primary cardiac arrest is largely indirect. This arises from the high prevalence of coronary artery disease in persons dying suddenly, varying definitions of "sudden," and inconsistencies in coding the causes of death in the absence of an autopsy.

In a Soviet series of 50 autopsies, 30 persons had died suddenly. All had had chronic alcoholism, and 17 of the 30 had substantial blood alcohol levels at the time of their death. Compared with control subjects who died of lethal alcohol intoxication, those dying suddenly had greater degrees of myocardial hypertrophy, fibrosis, and necrosis.[64]

Registration with the Swedish Temperance Board was associated with increased risks of sudden cardiac death in 50-year-old men observed prospectively for ten years.[65] Similarly, men who chose not to participate in the Göteborg Primary Prevention Trial were more often registered for alcohol problems and had a higher incidence of coronary artery disease deaths. The excess CAD mortality in nonparticipants was largely accounted for by sudden cardiac deaths.[6,66,67] In a longitudinal study of 50-year-old men in Uppsala, half of all men dying suddenly were registered at the Temperance Board.[68,69]

In a five-year Finnish study of 4,532 men aged 40 to 64 years, investigators found that the incidence of sudden death was much lower in abstainers, regardless of the presence of coronary artery disease. This reduced risk was more pronounced in the oldest age group and was true for both smokers and nonsmokers.[70]

The Framingham study reported an increased risk of "sudden death not preceded by definite clinical evidence" of coronary heart disease in persons drinking more than 90 oz per month.[71] A case-control study of sudden unexpected death in women in Rochester, Minnesota, showed that 40% of cases had a diagnosis of alcoholism compared with 6.8% of patients with myocardial infarction and 3.3% of controls.[72]

In a New Zealand study in which spouses of persons who had died suddenly were interviewed, alcohol intake was positively associated with the terminal event, although the investigators noted that persons dying within an hour of symptoms had lower weekly alcohol consumption than those dying later during the first day.[73]

Not all studies, however, have found a positive relationship between sudden death and alcohol intake. In the Kaiser-Permanente experience, "instantaneous" sudden cardiac death was no more likely in current drinkers than in those who were reported to have consumed no alcohol in the past year.[74]

Risk Indicators for Coronary Artery Disease and Stroke

Before considering the overall impact of alcohol on CAD and stroke incidence, the effects on individual risk factors for those diseases will be considered.

Blood Pressure

In 1915 Lian described the association of hypertension with alcohol intake, noting a higher prevalence in French army officers with the greatest alcohol consumption.[75] During the next several decades, however, the association was largely ignored.[76] In the past ten years, numerous studies have been conducted worldwide on alcohol-related hypertension.[77] The topic is complex, subject to all of the methodologic concerns mentioned earlier as well as a complex interaction with electrolytes and minerals[78] not discussed here.

Initial effects. In normotensive subjects who usually drank little or no alcohol, blood pressures rose slightly after drinking 1 gram per kg body weight for five days. The same was true in hypertensive light drinkers. In contrast, hypertensive subjects who had been consuming their usual moderate amounts of alcohol had a greater response to an alcohol challenge.[79]

A British study was done of male and female alcoholic patients with a mean age of 44 years. Each had a daily intake of more than 80 grams (mean, 196 grams). The average duration of heavy drinking was 15.8 years (range 2 to 50). The blood pressure (BP) was taken before cessation, during detoxification, and after two months of abstinence. The initial blood pressure exceeded 140/90 mm of mercury in more

than half of subjects. A significant linear positive correlation was noted between the initial blood pressure and the mean daily intake during the three months preceding admission. Withdrawal symptoms were most severe in those with the highest initial pressures. In most subjects, the BP fell to normal—mean, 137/87 to 122/77 mm of mercury—after detoxification and remained low—122/75 mm of mercury—in subjects who remained abstinent for a year or more. It rose again, however—128/81 to 144/89 mm of mercury—in those who resumed drinking alcohol.[80]

Evidence for the acute effects of alcohol on the blood pressure also comes from studies during withdrawal. Reducing alcohol intake in hypertensive men from six to eight drinks per day to none resulted in a decrease in systolic and diastolic pressure of 13 and 5 mm of mercury, respectively, over a three- to four-day period.[81] In another study, patients continued their usual antihypertensive medications during six weeks of usual drinking and six weeks of consuming only a low-alcohol beer. The mean alcohol consumption dropped from 452 ml per week to 64 ml per week. During the last two weeks of the low-alcohol period, the systolic and diastolic pressures had dropped 5 and 3 mm of mercury, respectively, from the usual drinking period.[82] In normotensive men, a decrease from three drinks per day to three drinks per week decreased the systolic BP by 4 mm of mercury but did not significantly change the diastolic pressure over a period of six weeks.[83]

Using a randomized, open crossover design, Howes studied normotensive persons previously consuming 10 to 40 grams of alcohol a day. Compared with four days of consuming 80 grams per day, subjects had drops of 8 and 6 mm of mercury in the systolic and diastolic BPs, respectively, after four days of abstinence.[84]

Long-term effects. Some have suggested that hypertension is at least twice as common in persons with alcoholism[85] and that alcohol use may be the most common cause of secondary hypertension.

Klatsky and co-workers studied blood pressure and usual drinking habits in 83,947 men and women who were members of Kaiser Permanente.[86] Participants were asked to report their alcohol consumption in one of three categories (drinks per day): two or less, three to five, and six or more. Men in the lowest category had BPs similar to control subjects, but women in the lowest category had BPs lower than controls. In both men and women, those reporting consuming three or more drinks daily had higher systolic and diastolic pressures and a higher prevalence of BPs of 160/95 mm of mercury or higher. These associations were independent of age, sex, race, smoking, caffeine use, former "heavy drinking," educational attainment, and adiposity. Compared with nondrinkers, persons consuming six or more drinks per day had a prevalence of hypertension that was doubled in whites and 1.5 times in blacks.[86]

The investigators also reviewed early Framingham data, noting that men who consumed 100 oz per month or more had mean systolic blood pressures 7 mm of mercury higher than lighter drinkers; hypertension—higher than 160/95 mm of mercury—was twice as prevalent in those who drank 60 oz or more per month compared with those drinking 10 to 29 oz per month.

In the Lipid Research Clinics Prevalence Study, systolic and diastolic pressures were both linearly related to alcohol intake. An analysis of regression coefficients suggested that a daily consumption of 30 ml would increase the systolic BP by 2 to 6 mm of mercury. Investigators also noted that an elevated BP was more strongly associated with past 24-hour consumption than with intake during the preceding six days.[87]

In a study of volunteer Australian men, a quarter of whom drank more than 50 ml a day, investigators found a linear increase of blood pressures with a mean daily alcohol consumption at increments of 1-mm-of-mercury systolic BP for each drink a day. The mean systolic BP was 5 mm of mercury higher in heavy drinkers than in nondrinkers. They also noted that heavy and moderate drinkers (53% of the study population) were both four times more likely to have a systolic BP of 140 mm of mercury or higher and three times more likely to have a diastolic BP of 90 mm of mercury or higher. Previous drinkers had blood pressures similar to those who never drank.[88] These relationships were noted for all levels of obesity, which is another powerful predictor of hypertension.[89]

The Stanford (California) Five City Project is a community health education study designed to reduce the prevalence of cardiovascular risk factors and the incidence of cardiovascular disease in entire communities. Subjects included 883 men and 959 women aged 20 to 74 years not taking blood pressure medications. The association of blood pressure and dietary alcohol was linear in all men and in women older than 49, particularly in those not taking replacement estrogens. Systolic BP effects were more pronounced than those of diastolic BP.[90]

Approximately half of reported studies have found a J-shaped relationship of alcohol use and blood pressure.[77] An analysis of the Tecumseh, Michigan, study data showed that the lowest blood pressures were associated with 1.5 drinks per week in men and about four drinks per week in women.[91] In at least one study, however, lighter drinkers were younger and leaner,[92] suggesting that the other health habits of light drinkers might also influence the blood pressure. But in other studies, the J-shaped curve was independent of those physiologic variables.[86,91]

Studies also differ in their "threshold" values—levels of alcohol consumption above which the blood pressure invariably rises. The Lipid Research Clinics study estimated this value to be 20 to 30 ml a day. In the Kaiser-Permanente study, this level was 90 ml a day[86]; a later investigation found a threshold in women only.[93] Other investigators found no threshold in either sex.[80,88]

Several investigators have found that alcohol effects on the blood pressure are greater in older persons,[87,90,93] but the Michigan investigators noted greater effects on the systolic blood pressure in persons aged 18 to 39.[94]

It is unclear whether the type of alcoholic beverage consumed is important. The later Kaiser study noted greater pressor effects from beer and liquor consumption than from wine, as did the Lipid Research Clinics study.[93,95] In an Italian study, however, wine drinkers had a higher prevalence of hypertension than nondrinkers of both sexes.[96]

Incidence. Investigators of the prospective Chicago People's Gas and Western Electric studies found that heavy alcohol users had greater increases in blood pressure than did nondrinkers.[97] Similar findings were obtained in the Zutphen (Netherlands) Study.[98] The Framingham Offspring Study also found a positive relation of blood pressure to alcohol intake in 4,294 men and women observed for eight years.[89]

Etiology. In a study of monozygotic and dizygotic twin pairs who were discordant for alcohol use, an association of blood pressure and alcohol use that was independent of genetic factors was noted.[99] Evidence for a direct pressor effect of alcohol is now fairly well established[83]; this may result from interference with central inhibitor pathways or through modified calcium transport.[88] Psychosocial stress is another possible contributor because it may raise both the level of alcohol consumption and the blood pressure.[100]

Adherence. Investigators have noted that persistent drinkers do not achieve as great an antihypertensive effect from drugs as do nondrinkers on the same pharmacologic regimen.[80] In a trial during which antihypertensive medications were withdrawn, persistent drinkers were much more likely to require the resumption of medication.[101] Others have noted that the cessation of alcohol drinking is often accompanied by a better adherence to a medication regimen.[102,103]

It is difficult to estimate the percentage of persons who have hypertension due solely to alcohol consumption. More important, however, is the public health effect of reducing moderate to high alcohol consumption in all hypertensive drinkers. While the blood pressure may fall after the cessation of drinking, it is not certain if alcohol-induced myocardial hypertrophy will be reversible.

Hemostasis

Alcohol ingestion may influence heart disease through hemostatic mechanisms.[104] In studies of healthy volunteers, Hillbom and co-workers noted an activation of the coagulation cascade, including decreased fibrinolytic activity, increased factor VII coagulant activity, and shortened bleeding times after excessive alcohol intake,[105] as well as increased platelet reactivity to adenosine diphosphate and associated formation of thromboxane B_2.[106]

In addition to coagulation abnormalities due to cirrhosis, habitual drinkers are at further risk. Thrombocytopenia is frequently found in heavy drinkers,[107] along with decreased platelet aggregability after acute ingestion[107,108] and during long-term use.[109-111] Investigators have noted decreased platelet counts in subjects during alcohol detoxification,[112] followed by rebound thrombocytosis.[112,113] Platelet hyperaggregability, unrelated to smoking or drug treatment, also occurs during withdrawal.[114,115]

Meade and associates have documented lower fibrinogen levels and increased thrombolysis with increased alcohol consumption.[109] Pikaar and colleagues provided four different daily doses of alcohol to normal (nonalcoholic) subjects during a five-week study. They noted a linear increase in plasminogen levels with increased alcohol intake, along with greatly reduced levels of tissue-type plasminogen activator. Collagen-induced platelet aggregation was reduced during alcohol consumption, while no change was observed in platelet aggregation induced by adenosine diphosphate, platelet secretion, or hematologic values.[111] In two other studies, bleeding time was prolonged within an hour after alcohol ingestion,[107,108] but others have found no effect on bleeding time.[115]

Lipids

The role of lipids and lipoproteins in coronary artery disease risk has been well established, but their influence on stroke risk is less well studied.[115] In most studies, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides are measured directly. Using the Friedewald formula[116] and estimating the levels of very-low-density lipoprotein (VLDL) cholesterol to be a fifth of those of triglycerides, low-density lipoprotein (LDL) cholesterol is calculated as follows,

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5.$$

Concentrations have been expressed in milligrams per deciliter in the United States, and efforts are now being made to have them expressed in millimoles per liter, as they are elsewhere.

Most epidemiologic studies show a direct correlation between CAD risk and total cholesterol, LDL-cholesterol, and triglyceride levels. Debate continues regarding the independent contribution of the triglyceride level to CAD risk. In a recent study, HDL cholesterol appeared to account for most of the triglyceride-CAD association.[117]

High-density-lipoprotein cholesterol has two main subfractions, HDL_2 and HDL_3 cholesterol. The former has been inversely associated with the risk of coronary disease in most studies, but only recently has HDL_3 cholesterol been found to be an important predictor of a reduced CAD risk.[118,119] Apolipoproteins may be better indicators of the CAD risk; apolipoprotein A-I is inversely associated with coronary artery disease, and apolipoprotein B is directly correlated.

The influence of alcohol on lipid, lipoprotein, and apolipoprotein levels depends in part on drinking patterns and accompanying liver damage.[120] Triglyceride levels are positively related to alcohol intake, even after adjusting for obesity and serum cholesterol level,[121,122] probably due to increased secretion of VLDL from the liver. The total cholesterol effects of alcohol often represent the relative effects of LDL cholesterol (no effect or slightly decreased levels) and HDL cholesterol (usually an increase). Dietary factors play an important role in LDL levels, making analysis of studies in alcoholic patients difficult if accurate nutritional information cannot be obtained. Some have suggested that the apparent protective effect of alcohol against coronary artery disease may be applicable only in those consuming high amounts of dietary cholesterol or saturated fat.[5]

Much attention in recent years has focused on alcohol and HDL cholesterol. The excitement engendered by reports of both lower coronary artery disease rates in persons with high HDL-cholesterol levels and higher HDL-cholesterol levels with increased alcohol consumption was dampened somewhat after the results of fractional analyses of HDL cholesterol were reported. In most studies of nonalcoholic persons, the alcohol-induced rise occurs in the HDL_3-cholesterol subfraction, which, until recently, was not thought to exert a CAD protective effect.[5,123] In a study of 234 alcoholic persons, Dai and co-workers noted an increase in both HDL-cholesterol subfractions with increasing alcohol intake until 450 ml of daily consumption, after which both total HDL- and HDL_2-cholesterol levels decreased. Alcoholic subjects with liver disease had higher levels, and HDL-cholesterol levels and those of both subfractions decreased considerably during a month of abstinence,[124] an observation shared by others.[123,125,126] Possible pathways relating HDL cholesterol and alcohol include mediation through sex hormones, as reflected in increased HDL-cholesterol levels in women and decreased testosterone levels in alcoholic men, increased degradation of VLDL, and mediation through microsomal

enzyme induction in the liver.[124] In one study, cessation after long-term drinking resulted in decreases in HDL-cholesterol and lipoprotein lipase activity of approximately 40%.[127]

Experimental studies of moderate alcohol consumption on apolipoprotein levels generally show a relationship of intake and increased apolipoprotein A-I levels.[128,129] This effect can be seen in alcohol doses as small as one drink per day.[130] In studies of alcoholism, Avogaro and colleagues described decreased apolipoprotein A-I levels in patients with liver disease,[131] and two other investigations noted decreased A-I levels after alcohol withdrawal.[127,132]

Thus, it appears that mild to moderate alcohol consumption is associated with more favorable lipid and lipoprotein profiles and a reduced risk of coronary artery disease, although the mechanisms underlying these associations remain unclear. Heavier consumption leading to alcohol abuse and coexisting liver impairment is associated with adverse lipid and lipoprotein profiles and increased coronary artery disease risk.[133]

Smoking

Because the heaviest drinkers are often heavy smokers, the possibility that the alcohol-coronary artery disease association is due solely to tobacco consumption must be eliminated. While the earliest studies did not control for smoking, more recent trials have done so, establishing an independent role for heavy alcohol use in patients with coronary disease.[67] A study of twins confirmed an incidence of coronary artery disease and stroke deaths in heavy drinkers, regardless of smoking status. The Multifactor Primary Prevention Trial in Göteborg found the CAD risk to be highest in those who smoked and drank—the relative risk being 4.2 compared with that in nonsmoking nondrinkers.[67]

Benowitz and co-workers studied the cardiovascular responses of normal subjects to the oral ingestion of alcohol and the intravenous administration of nicotine. Ethanol administration raised the heart rate, systolic blood pressure, and their product, and nicotine had an additive effect on the heart rate and the rate-pressure product. The vasoconstricting effect of nicotine was antagonized by alcohol. They concluded that the combined effects could contribute to dysrhythmias in patients with coronary artery disease.[134]

Coronary Artery Disease

Myocardial ischemia can result from any or a combination of the following processes in the coronary arteries: atherosclerosis, vasospasm, thrombosis, and emboli. The effects of alcohol on these processes, as well as the multiple indicators of CAD risk, have been discussed earlier. In the aggregate, it appears that the alcohol-CAD relationship is dose-dependent. In heavy drinkers—such as drinking six or more drinks per day, or being registered with temperance boards—coronary artery disease mortality (particularly sudden death) is increased. At mild to moderate levels of intake, however, evidence suggests no elevation in the CAD risk.

Heavy Drinkers

Several studies in the United States have documented the increased risk of consuming six or more drinks a day. In Chicago Dyer and associates noted that this increased risk persisted even beyond the first ten years of surveillance.[135] British men drinking more than five drinks per day had higher coronary artery disease incidence rates than lighter drinkers.[136] Investigators in a Massachusetts study showed an increased risk from consuming more than 34 grams per day.[137] Similar results were obtained in a New Zealand study, particularly for sudden cardiac death.[73] In a Swedish study, persons not registered with the temperance board had the lowest coronary disease rates. In comparison, the incidence in all those registered was doubled; for the heaviest drinkers, rates were three times higher.[66]

Nondrinkers

Persons not currently consuming alcohol include lifelong teetotalers and ex-drinkers. In most studies, ex-drinkers have significantly higher CAD rates than those who never drank. In the Tecumseh study, their risk was threefold compared with that for drinkers and teetotalers.[121] Wannamethee and Shaper point out that ex-drinkers have the highest prevalence of angina, electrocardiographic evidence of myocardial infarction, and self-reports of poor health; their standard CAD risk indicators are no more favorable than in other groups.[3]

Mild to Moderate Drinkers

In most cross-sectional studies, persons who drink alcohol but consume less than six drinks per day are less likely to have coronary artery disease than nondrinkers and heavier drinkers.[138,139] These findings were confirmed in prospective studies, including those from Hawaii,[140–142] Japan,[142] Massachusetts,[71] Puerto Rico,[143] London,[144] eastern Finland,[145] and Yugoslavia.[146] Study designs, however, often have not differentiated between ex-drinkers and those who never drank. The British Regional Heart Study made such a differentiation, examining men who did not have preexisting cardiovascular-related conditions. In that population, nondrinkers were at minimal risk, suggesting that the apparent benefits of consuming as many as five drinks per day may have been overemphasized.[147] In contrast, teetotalers free of clinical heart disease or other major recent illnesses who were part of the Kaiser-Permanente prepaid health plan had a higher rate of hospital admissions for coronary artery disease than ex-drinkers or current drinkers.[93]

Stroke

Within the past ten years, mortality from stroke has been almost halved in Japanese women and men and in men in the United States,[148] suggesting that the risk may be modifiable for both brain infarcts and hemorrhages. Although survival after a stroke has improved,[149] the stroke incidence has decreased more dramatically.[150] During the past 30 years, the relationship of alcohol abuse and stroke has been firmly established.[115]

The observed decreased regional cerebral blood flow in persons with both short- and long-term excessive alcohol intake[151] has been attributed to altered cerebral metabolism and to vasospasm of cerebrovascular smooth muscle. These effects, combined with those of alcohol-related disorders of blood pressure, coagulation, and cardiac rhythm discussed earlier, place heavy drinkers at a greater risk of stroke.[104]

Brain infarcts, which result primarily from underlying atherosclerotic cerebrovascular disease and from thromboembolism, are increased in incidence with heavy alcohol use.[152] Smoking, which frequently accompanies heavy alcohol use, has a detrimental effect on both atherosclerosis and clotting.

Hemorrhagic strokes may result from either subarachnoid hemorrhage due to the rupture of a circle of Willis aneurysm or from intraparenchymatous bleeding. The latter condition is usually associated with hypertensive changes in small penetrating arteries deep within the brain.[150] Because of its hemostatic effects, alcohol use increases the probability of hemorrhagic stroke.[140]

The relative proportions of infarct and hemorrhage in stroke cases vary with racial categories, often reflecting differences in risk factors. For example, hemorrhagic strokes constituted approximately 30% of strokes among Japanese-Hawaiian men,[153] but in the Framingham study, the percentage was only 15%.[150]

In addition to high blood pressure, hemostatic factors, and smoking, other possible causes of stroke more common in alcoholic patients include cardiac dysrhythmias and cardiomyopathy, as discussed earlier. In addition, alterations in cerebral blood flow and autoregulation occur with habitual alcohol intake.[104,154] These changes may result from the toxic effects of alcohol on cerebral metabolism and its direct vasospastic effects on cerebrovascular smooth muscle.[15]

The direct association of alcohol consumption and stroke has been noted in studies from many countries, including Japan,[155] Hawaii,[156,157] Yugoslavia,[146] the United Kingdom,[154] the US,[158] and Finland,[115] particularly in persons younger than 50.[105,158]

Investigators from the Honolulu Heart Study found that the stroke rate in heavy drinkers was elevated, regardless of blood pressure levels. They noted that consuming greater than 30 ml per day doubled the stroke risk.[157]

In the Yugoslavia Cardiovascular Disease Study, Kozarevic and colleagues compared heavier drinkers with those drinking only weekly; stroke rates were doubled in daily drinkers and tripled for those having two or more drinks per day.[146]

In a case-control study from Birmingham, England, light drinkers—10 to 90 grams per week—had only half the stroke rate of nondrinkers. In contrast, those men consuming 300 grams or more a week had a relative risk of 4.2 compared with nondrinkers.[154]

Hillbom noted the precipitation of both hemorrhagic and infarction strokes during intoxication rather than withdrawal in heavy drinkers by comparing stroke rates during different days of the week in those with and without alcohol ingestion within the 24 hours preceding the event. He and his coworkers also found that the incidence of alcohol-related strokes parallels the relative alcohol consumption in Finnish women and men, but the sex ratio in alcohol-unrelated strokes was nearer unity.[115]

Infectious Endocarditis

Buchbinder and Roberts found that of 59 patients with fatal active infective endocarditis, 14 (24%) had chronic alcoholism. Frequently the endocarditis was associated with pneumonitis or meningitis, an observation rarely mentioned in the medical literature since its initial description more than 100 years ago.[159] In a clinical and postmortem study, Snyder and co-workers found an increased concurrence of cirrhosis and bacterial endocarditis.[160] Of course, the prevalence of alcoholism in patients with any disease will depend on the population sampled, but the association between alcohol abuse and endocarditis appears to be both real and important.

Fetal Heart

Maternal heavy drinking can produce an alcohol embryopathy with characteristic defects in the atrial and ventricular septa.[161,162] In a prospective study of 1,016 children with congenital heart disease, 27 cases of embryopathies were defined. While 13 of the 27 were due to rubella infection, 10 resulted from maternal alcoholism.[163]

These findings add to those of many other studies of the fetal alcohol syndrome and have led most authorities to recommend that women abstain from drinking during pregnancy.[164]

Policy Implications

It appears that an average of one drink per day and the avoidance of binge drinking do not pose a significant additional risk for cardiovascular disease beyond abstinence in otherwise healthy adults.[77,82] The risks for alcoholic cardiomyopathy and an exacerbation of cardiac dysrhythmias, however, are clearly related to the amount of alcohol consumed. Coupled with the potential for alcohol abuse, these considerations preclude any recommendation for persons to begin drinking.

The risk of fetal cardiac abnormalities related to maternal drinking suggests a policy of abstinence for pregnant women.

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Medical Staff Conference

Therapeutic Options in Treating Acute Myocardial Infarction

Discussant
JOHN W. DANFORTH, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Acute myocardial infarction remains a devastating illness, but research over the past decade has shown that the initial and long-term outcome of coronary occlusion can be altered by immediate therapy. John Danforth, MD, will review the underlying rationale, the outcome, and his suggested guidelines for treatment in the hours after an acute myocardial infarction.*

JOHN W. DANFORTH, MD†: In the past 12 years we have witnessed unparalleled progress in treating the acute myocardial infarction patient. A number of promising therapeutic options were introduced, including thrombolytic therapy, emergent angioplasty, and immediate-intervention β-blockade therapy. For the first time, these interventions enabled physicians to substantially influence the pathophysiology of this disorder. As the benefits of immediate-intervention therapy became evident, the philosophy of treating an acute myocardial infarction changed dramatically—from expectant observation to relatively aggressive intervention.

Now the medical community is attempting to tackle the controversies that have evolved in the wake of this recent departure from convention. At present, the rationale for immediate-intervention therapy is well accepted. Considerable uncertainty persists, however, regarding the relative merits of the various therapeutic options that have become available. Although a definitive resolution of these issues must await the completion of several ongoing trials, there are enough data to draw preliminary conclusions about the value of some of these interventions. I will review these conclusions and apply them to the development of a preliminary treatment strategy for patients with acute myocardial infarction.

Thrombolytic Therapy

There is little debate that thrombolytic therapy is the cornerstone of treatment for an acute myocardial infarction. The timely administration of thrombolytic therapy consistently has been shown to reduce both infarct size and postinfarction mortality.[1] Although thrombolytic therapy is now considered the standard of care in treating an acute myocardial infarction, there is little consensus on the agent of choice. To understand the issues that have contributed to this uncertainty requires an appreciation of the limitations of thrombolytic therapy in general.

We now recognize that thrombolytic therapy at best permits the salvage of a modest fraction of the myocardium in the region at risk for infarction. This circumstance derives from several facts:

- Myocardial necrosis occurs rapidly with sustained oxygen deprivation;
- Patients frequently seek medical attention late in the course of an infarction; and
- Necrosis probably continues unabated for 30 to 60 minutes following the intravenous administration of a thrombolytic agent.

Although unknown, current speculation maintains that an acute myocardial infarction becomes complete in humans within 4 to 12 hours (mean, 6 hours) following the onset of symptoms. This variation among patients probably reflects the effects of many factors, including heart rate, afterload, and collateral blood flow, on the rate of necrosis development. These presumptions have been extrapolated from the results of studies in animals. An acute infarction is completed within two hours in pigs[2] and within six hours in dogs.[3] Because the extent of native collateral development in humans is intermediate between that of pigs and dogs, it is reasonable to presume that the time to completion of an acute infarction among patients with limited secondary collateral development varies between two and six hours. This probably underestimates the time course of most acute infarctions, however, because many patients have evolved secondary collaterals within the infarct zone. Taken together, these observations suggest that the time course for an acute infarction varies from 4 to 12 hours in patients who survive the initial event.

The rapidity with which necrosis develops following an acute myocardial infarction stems from the poor development of the hexose monophosphate shunt within the heart and the heart's relatively high oxygen extraction ratio.[4] The heart

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ABBREVIATIONS USED IN TEXT

GISSI II = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [trial], phase II
ISIS-2 = Second International Study of Infarct Survival
rt-PA = recombinant tissue plasminogen activator
TAMI = Thrombolysis Angioplasty in Myocardial Infarction [study group]
TIMI I and II = Thrombolysis in Myocardial Infarction [trial], phases I and II
UCSF = University of California, San Francisco

is incapable of sustained anaerobic metabolism and cannot respond to an ischemic insult by recovering more oxygen from a limited blood supply.[4] In short, the heart cannot tolerate sustained oxygen deprivation, and necrosis develops rapidly in this circumstance.

Given the rapidity with which necrosis develops within the infarct zone and the propensity of patients to seek medical attention relatively late in the course of an acute myocardial infarction, it is reasonable to presume that extensive necrosis has already occurred in most patients by the time thrombolytic therapy can be administered (Figure 1), and necrosis probably continues for a limited time even after thrombolytic therapy is given. With respect to this latter issue, it develops that thrombolysis is a time-dependent process. According to the results of phase I of the Thrombolysis in Myocardial Infarction (TIMI I) trial,[5] for example, recannalization commonly develops 30 to 90 minutes following the intravenous administration of thrombolytic therapy (Figure 2). These facts suggest that for most patients the myocardial salvage potential of thrombolytic therapy is limited.

It is precisely this situation that has hampered efforts to compare the clinical usefulness of the various thrombolytic agents that have become available. For example, we now recognize that the thrombolytic efficacy of recombinant tissue plasminogen activator (rt-PA) is probably superior to that of streptokinase.[5-12] To date, two studies have been published comparing the relative efficacy of these agents: the TIMI I trial[5] and the European Cooperative Study.[6] The data favor the use of rt-PA versus streptokinase (Figure 3). In addition, the acute recannalization data derived from virtually all the single-drug, placebo-controlled trials reported to date indicate that rt-PA is superior to streptokinase from the standpoint of the initial thrombolytic efficacy (Figure 3).[7-12]

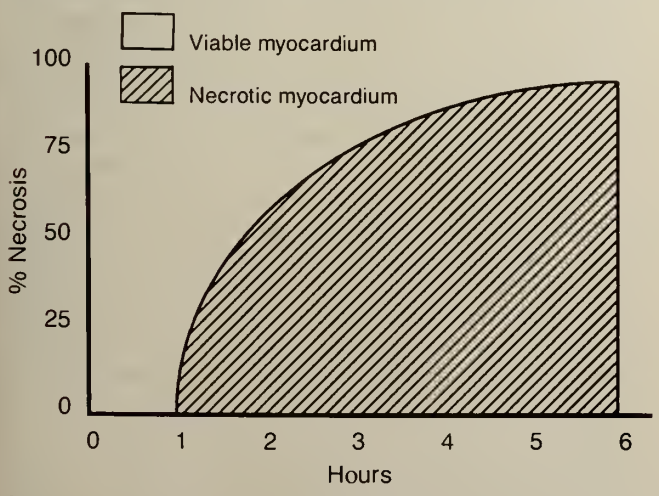

Figure 1.—A hypothetical myocardial necrosis curve is shown, indicating the portion of the infarct zone that sustains irreversible damage in the hours after coronary occlusion.

Despite the higher early recannalization rates reported following the administration of rt-PA versus streptokinase, it has not been proved that rt-PA has a higher potential for preserving myocardium. For example, the timely administration of both agents appears to confer a similar effect on the left ventricular ejection fraction (Table 1).[7,9,10,13-19] The TIMI I trial is perhaps the best example of this disparity.[5] This study was designed to compare the thrombolytic and myocardial salvage potential of intravenous rt-PA versus intravenous streptokinase. The results indicated that the thrombolytic rate for rt-PA was twice the corresponding rate for streptokinase: 62% versus 31%. Yet the data suggested that the myocardial salvage potential of the two agents was similar.[18]

In retrospect, it seems likely that the relatively prolonged delay to therapy in this study (mean, 5.3 hours) accounts for this disparity. If one assumes that an infarct becomes com-

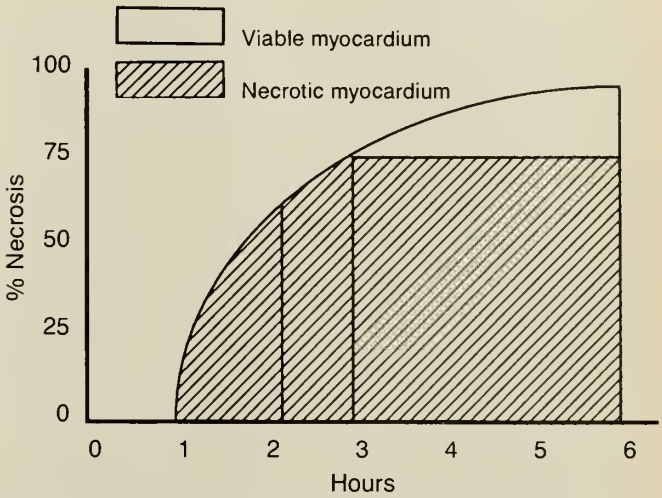

Figure 2.—The graph shows the myocardial salvage potential of thrombolytic therapy administered two hours after coronary occlusion. Thrombolysis occurs 30 to 90 minutes after drug administration, and necrosis probably continues until recannalization is achieved.

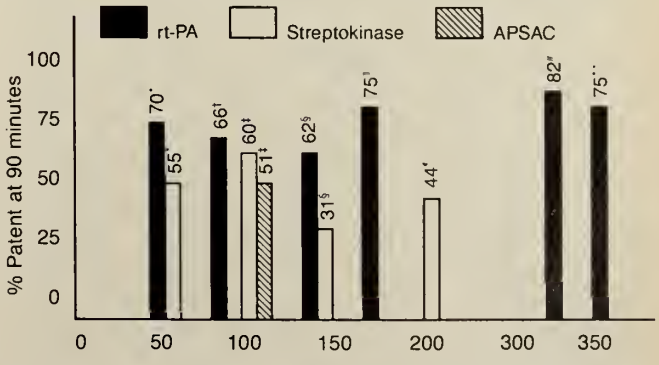

Figure 3.—Recannalization rates following intravenous thrombolytic therapy were determined by coronary arteriography that was done within 90 minutes. The studies are presented in order of size and are identified by footnote symbols. The juxtaposition of bars indicates that two agents were administered on a randomized basis in the same trial.

APSAC = anisoylated plasminogen streptokinase activator complex, rt-PA = recombinant tissue plasminogen activator
*From Verstraete et al[6]; rt-PA: 64 patients, streptokinase: 65 patients.
†From Guerci et al[9]; 72 patients.
‡From the APSAC trial[12]; streptokinase: 111 patients, APSAC: 115 patients.
§From the TIMI I trial[5]; rt-PA: 143 patients; streptokinase: 147 patients.
‖From the TIMI IIA Research Group[10]; 192 patients.
¶From Stack et al[11]; 216 patients.
#From the TIMI II pilot study[8]; 317 patients.
**From the TAMI study group[7]; 386 patients.

TABLE 1.—*Effect of Immediate-Intervention Angioplasty on In-hospital Mortality*

Trial	*Patients, No.*	*Immediate Angio-plasty, %*	*Deferred Angio-plasty, %*
TAMI, 1987[7]	197	4	1
European Cooperative, 1988[19]	367	7	3
TIMI IIA, 1988[10]	389	8	5

TAMI=Thrombolysis Angioplasty in Myocardial Infarction study group, TIMI IIA=Thrombolysis in Myocardial Infarction trial, phase IIA

plete within six hours after the start of symptoms and that an hour is required to achieve thrombolysis following the administration of therapy,[5] then it is reasonable to assume most patients enrolled in the TIMI I trial probably had a completed infarction before thrombolysis was accomplished. In this circumstance, one would not expect recannalization to influence the extent of necrosis.

Although the TIMI I trial was an exceptionally late-entry trial, it is likely that the previous considerations probably apply to the interpretation of much of the data generated on the clinical use of thrombolytic therapy. Taken together, the current data indicate that rt-PA is a superior thrombolytic agent relative to streptokinase, and yet both agents appear to have the same effect on the global left ventricular ejection fraction.[5-17] Although the imprecision of left ventriculography may partially account for this disparity, it is still reasonable to presume that most of the myocardium within an infarct zone had probably sustained irreversible damage before thrombolysis could be achieved in most patients in these trials and that this circumstance limits the potential difference between these two agents in preserving myocardium.

Every effort must be made to deliver these agents as early as possible during the course of an infarction. Investigators for the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial reported that the possible effect of the use of streptokinase on postinfarction mortality was inversely related to the time delay to therapy.[20] According to the results of this trial, administering streptokinase within an hour following the start of symptoms was associated with a 46% reduction in postinfarction mortality ($P<.0001$), whereas administering this agent five hours thereafter did not significantly influence mortality.[20] Topol and colleagues showed that the myocardial salvage potential of thrombolytic therapy is similarly dependent on the time delay to therapy.[21] These investigators reported that the mean left ventricular ejection fraction of patients treated with rt-PA a mean of 3.9 hours after the onset of symptoms was substantially lower (51% ± 10%) than the corresponding ejection fraction of persons who received therapy within 2 hours after the start of symptoms (56% ± 9%).[21]

Despite the obvious implications of these data, it is clear that an enormous effort will be required to speed the delivery of therapy for acute myocardial infarction. We will need to develop large-scale educational programs that will encourage patients to seek medical attention during the early phase of an infarction. Diagnostic tools for the rapid detection of an acute infarction will have to be refined. Steps will need to be taken in hospitals to minimize the delay before therapy is given to patients who present with an acute infarction. Programs probably will need to be developed for the administration of thrombolytic agents in the field in rural communities with prolonged ambulance "scoop and carry" times.

It appears that thrombolytic therapy confers about a 10% to 20% reduction in infarct size[22] and a 2% to 3% reduction in postinfarction mortality. The second figure is based on a mean six-week postinfarction mortality rate for 10% to 12% of patients who survive long enough to receive medical attention and a relative 20% to 30% reduction in mortality following the administration of single-drug thrombolytic therapy. Virtually all mortality data are now reported in terms of a percent of a percent, and this convention can be misleading.

Adjuvant Therapy

Angioplasty

Given the limitations of thrombolytic therapy, considerable effort has been directed toward developing interventions that can be administered in conjunction with thrombolytic therapy to further contain the formidable morbidity and mortality of an acute infarction. Of the various interventions proposed, emergent angioplasty was originally considered one of the most promising. It was thought that this procedure might limit the development of necrosis regardless of a patient's response to thrombolytic therapy. Among those who did not respond—in whom recannalization failed to occur, for example—it was hoped that angioplasty might permit the salvage of viable myocardium within the region at risk for necrosis.[23] Among those who did respond, it was hoped that angioplasty might offset the continued necrosis that probably occurs for a brief time following recannalization.

An imbalance between the myocardial oxygen supply and the demand probably persists for hours to days among the majority of patients who respond favorably to thrombolytic therapy. The myocardial oxygen demand remains substantially increased because sympathetic stimulation of the heart continues for several days after an infarction.[24] Similarly, the supply of myocardial oxygen probably remains depressed in the region at risk because blood flow within the infarct-related vessel is probably compromised by the presence of residual thrombous formation that may persist for days to weeks following recannalization.

Although there is little direct evidence to confirm the presumption that intracoronary thrombi commonly persist following recannalization, it is intriguing to note that the severity of infarct-related lesions identified immediately following recannalization tends to decrease over time.[7,19] Given the improbability that atheromas can undergo spontaneous autolysis, it is likely that this phenomenon reflects thrombolysis of clot superimposed on the infarct-related lesion. We now recognize that, among unstable angina patients, thrombus accumulation occurs commonly in the vicinity of an intracoronary plaque and that this thrombus is angiographically indistinguishable from underlying atheroma.[25] The presence of this thrombus commonly contributes to the apparent severity of stenotic lesions considered responsible for the development of ischemia among these patients.[24] In retrospect, it is likely that the presence of superimposed clot formation accounts for the observation that the severity of infarct-related lesions tends to diminish with time.[26,27] It is reasonable to assume that this thrombus impairs blood flow and compromises oxygen supply to the region at risk for infarction.

Myocardial oxygen demand probably remains high and

the supply low for hours to days following an acute event among most patients who respond favorably to thrombolytic therapy. As a result, it seems likely that myocardial ischemia and possibly necrosis continue for a limited period following recannalization. We may speculate that doing an emergent angioplasty might offset this imbalance and permit the further containment of an acute infarction. There is some evidence from studies of animals to suggest that ablation of an infarct-related lesion reduces infarct size relative to recannalization alone.[28]

The clinical experience with immediate angioplasty, however, has been discouraging. The mortality rates for every randomized trial reported to date have been consistently higher among patients receiving immediate angioplasty (Table 1).[7,19,29] The results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial[7] and the European Cooperative trial[19] indicated that immediate angioplasty increased the risk for reocclusion among patients who had responded favorably to thrombolytic therapy. The results of the TAMI trial further indicated that among patients who had not responded to thrombolytic therapy, salvage angioplasty did not influence the infarct size.[23] More recently, the results of phase II of the Thrombolysis in Myocardial Infarction (TIMI II) trial indicated that performing an angioplasty three days after an infarction provided no benefit relative to conservative therapy in reducing postinfarction morbidity and mortality.[30] Among patients presenting with shock, however, immediate angioplasty has been shown to reduce postinfarction mortality.

At present, there is no consensus on the role of immediate angioplasty in the treatment of an acute infarction. The results have been mixed, and considerable data suggest that this procedure is counterproductive in the setting of an acute infarction. Although the role of emergent angioplasty in treating an acute myocardial infarction remains to be determined, it is probably reasonable to conclude at this juncture that the benefit of this procedure is less than what was anticipated. Given our current uncertainty, this procedure probably should be reserved for patients enrolled in rigidly controlled trials; doing this procedure on a routine basis is not warranted. Considerable pathophysiologic evidence suggests that angioplasty may even be counterproductive. We now suspect that infarction is often precipitated by the rupture of an atheromatous plaque.[31] This process appears to cause the release of procoagulant factors into the systemic circulation, which presumably enhances the thrombolytic potential of the ruptured endothelial surface.[32,33] The interaction between a thrombogenic circulation and the prothrombotic endothelial surface presumably culminates in the development of an intravascular thrombus.

If this mechanism does account for acute infarction, then it is entirely conceivable that an angioplasty carried out during the early phase of an acute myocardial infarction might aggravate this condition. Balloon-mediated angioplasty is accomplished by creating multiple microscopic dissections within the atheromatous lesion subjected to mechanical dilatation. Most of these dissections are small—well below the power of resolution of conventional angiography. As a result, they often evolve without detection. While they are well tolerated under normal circumstances, it is conceivable that the creation of these microdissections during a phase of enhanced coagulation might predispose a patient to rethrombosis and hence reocclusion. In several trials of emergent angioplasty, reocclusion occurred with such frequency in patients who have responded favorably to thrombolytic therapy that the investigators have recommended withholding emergent percutaneous transluminal coronary angioplasty from these patients.[7,19]

Although immediate angioplasty cannot be recommended at this juncture, it is intriguing to speculate that the development of more effective platelet inhibitors might unmask benefits of the procedure in the initial treatment period. Several promising agents are currently undergoing preclinical trials,[34,35] and the introduction of these agents may revitalize the original enthusiasm for this promising procedure.

Aspirin

Given the current consensus regarding the pathogenesis of an acute myocardial infarction, aspirin should offer effective therapy (Figure 4). The results of the Second International Study of Infarct Survival (ISIS-2) trial indicate that administering aspirin alone is associated with a 22% reduction in postinfarction mortality.[36] The results of this and other trials indicate that aspirin also enhances the therapeutic potential of both rt-PA and streptokinase (Figures 5 and 6). For these reasons, aspirin therapy is strongly recommended.

β-Blockers

The results of the TIMI II trial strongly favor the administration of β-blockers in conjunction with thrombolytic therapy during the acute phase of an infarction.[30] They showed that conventional doses of intravenous or oral metoprolol tartrate given during the early phase of an acute infarction resulted in a 27% reduction in the incidence of postinfarction ischemia compared with giving aspirin and rt-PA alone, and that intervention with this agent within two hours after the start of symptoms resulted in a 58% reduction in morbidity and mortality at six weeks after an infarction compared with giving aspirin and rt-PA alone.

In retrospect, it seems logical that thrombolytic and β-blockade therapy should be synergistic in treating an acute infarction. Thrombolytic agents enhance the myocardial ox-

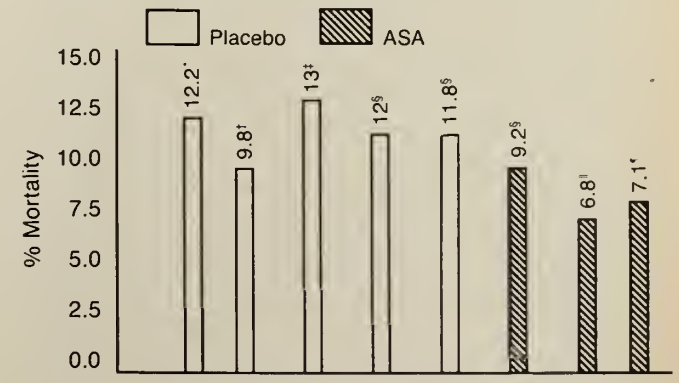

Figure 4.—The effect of aspirin therapy on absolute mortality 21 to 30 days after a myocardial infarction is shown in control groups. Mortality rates among the control groups of major placebo-controlled trials of thrombolytic therapy are indicated by the open bars. The hatched bars refer to studies in which the control groups received aspirin.

*From the AIMS Trial[38]; 502 patients.
†From Wilcox et al[39]; 2,490 patients.
‡From Gruppo Italiano[20]; 5,852 patients.
§From the ISIS-2 trial[36]; placebo: 8,595 patients, 8,600 patients; aspirin: 8,592 patients.
‖From the European Cooperative Study Group[22]; 366 patients.
¶From the ISAM Study Group[40]; 463 patients.

ygen supply, and β-blocking agents reduce the myocardial oxygen demand. Given that thrombolysis is a time-dependent process,[5] the early administration of β-blocking agents probably delays the onset of necrosis and thus enhances the salvage potential of thrombolytic therapy (Figure 6). Studies have shown that the rate of development of necrosis within the myocardium of animals varies in response to changes in the heart rate.[42] Specifically, necrosis develops more slowly in animals with lower heart rates.[42] The effectiveness of adjuvant β-blockade therapy, therefore, will probably depend on the heart rate or the cross product of a patient, or both. Patients presenting with tachycardia should derive the greatest benefit from β-blockade therapy and should be treated aggressively. Conversely, it is unlikely that administering β-blocking agents will confer significant benefit in persons with a relatively low cross product.

Nitrates

In theory, the use of nitrates should enhance the myocardial salvage potential of thrombolytic agents. Administering nitrates has been shown to enhance collateral blood flow in the regions subserved by an occluded vessel in both humans[43] and animals,[44] and it is reasonable to presume that collateral blood flow delays the onset of necrosis within the potential infarct zone. In this regard, the results of the TIMI I trial, a particularly late-entry trial, showed that myocardial preservation with thrombolytic therapy occurred only in patients with angiographic evidence of collaterals.[5] In retrospect, these results suggest that the presence of collaterals extended the window of opportunity for thrombolytic therapy, and this conclusion, in turn, supports the hypothesis that collateral blood flow delays the onset of necrosis. If so, and if nitrates enhance the amount of collateral flow within the region at risk, then they should be synergistic with thrombolytic agents in preserving the myocardium. There are no clinical data to support this contention, however. Of interest is that in a 1988 study, nitrates were found to significantly reduce postinfarction mortality.[45]

Calcium Channel Blockers

At present, calcium channel blockers have little or no role in managing the acute phase of a myocardial infarction.[46] Administering nifedipine has been shown to enhance mortality,[47] infarct size,[48] and reinfarction rate.[48] The adverse effect of nifedipine presumably stems from its propensity to provoke a reflex tachycardia. The administration of diltiazem hydrochloride during the postinfarction period is well tolerated but has not been shown to reduce mortality when administered routinely to patients after an infarction.[49] Conversely, one trial has shown that administering diltiazem reduces the risk of progression from a non-Q wave to a Q wave infarction.[50] However, the agent was given 24 hours after hospital admission. The role of diltiazem in the treatment of the acute phase—that is, the first 6 to 12 hours—of an infarction is unclear, and it should not be administered in lieu of nitrates or β-blocking agents until data are presented to the contrary. Diltiazem, like nifedipine, lowers blood pressure and thus might preclude the administration of β-blockers or nitrates, which appear more effective in this circumstance.

Lidocaine

The results of a 1988 analysis[51] indicate that the administration of lidocaine is associated with an increased risk of death after a myocardial infarction. Although the subject of considerable controversy, it is probably reasonable to conclude that lidocaine prophylaxis should not be administered routinely to the postinfarction patient.

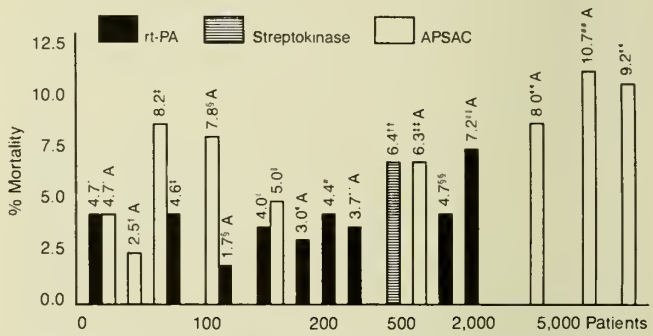

Figure 5.—Mortality rates are shown for the treatment groups of major trials of thrombolytic therapy 21 to 30 days after myocardial infarction. Studies are presented in order of size. The letter *A* indicates that aspirin was administered in conjunction with thrombolytic therapy.

APSAC = anisoylated plasminogen streptokinase activator complex, rt-PA = recombinant tissue plasminogen activator
*From Verstraete et al[6]; rt-PA: 64 patients, streptokinase: 65 patients.
†From White et al[15]; 79 patients.
‡From the Plasminogen Activator Italian Multicenter Study Group[41]; streptokinase: 85 patients, rt-PA: 86 patients.
§From White et al[17]; streptokinase: 110 patients, rt-PA: 115 patients.
‖From TIMI, phase I[5]; rt-PA: 143 patients; streptokinase: 147 patients.
¶From the European Cooperative Study Group[19]; 184 patients.
#From TIMI, phase II[8]; 317 patients.
**From the European Cooperative Study Group[22]; 355 patients.
††From the AIMS Trial Study Group[38]; 502 patients.
‡‡From the ISAM Study Group[40]; 859 patients.
§§From the TIMI II Study Group[30]; 1,626 patients.
‖‖From the Anglo-Scandinavian Study of Early Thrombolysis[39]; 2,516 patients.
¶¶From the ISIS-2 Collaborative Group[36]; with aspirin: 4,292 patients, without aspirin: 8,592 patients.
##From Gruppo Italiano[20]; 5,860 patients.

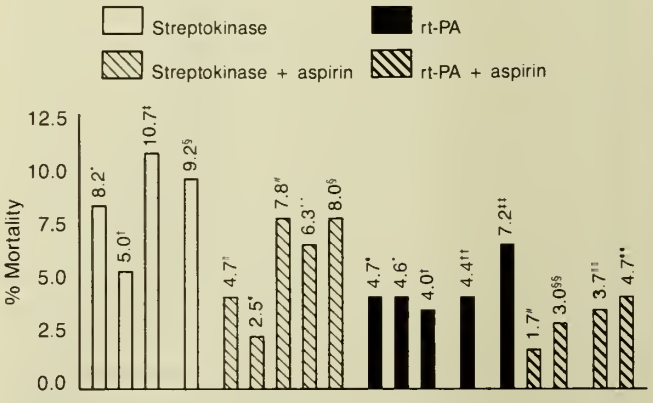

Figure 6.—Effect of aspirin therapy on postinfarction (21 to 30 days) mortality is shown for patients receiving thrombolytic therapy. The data contained in Figure 5 are here regrouped according to treatment regimen and are presented in order of increasing size of the study group.

rt-PA = recombinant tissue plasminogen activator
*From the Plasminogen Activator Italian Multicenter Study Group[41]; streptokinase: 85 patients, rt-PA: 143 patients.
†From TIMI, phase I[5]; streptokinase: 147 patients, rt-PA: 143 patients.
‡From Gruppo Italiano[20]; 5,860 patients.
§From the ISIS-2 Collaborative Group[36]; streptokinase: 8,592 patients, streptokinase plus aspirin: 4,292 patients.
‖From Verstraete et al[6]; streptokinase plus aspirin: 65 patients, rt-PA: 64 patients.
¶From White et al[15]; 79 patients.
#From White et al[17]; streptokinase plus aspirin: 110 patients, rt-PA plus aspirin: 115 patients.
**From the ISAM Study Group[40]; 859 patients.
††From TIMI, phase II[8]; 317 patients.
‡‡From the Anglo-Scandinavian Study of Early Thrombolysis[39]; 2,516 patients.
§§From the European Cooperative Study Group[19]; 184 patients.
‖‖From the European Cooperative Study Group[22]; 355 patients.
¶¶From the TIMI II Study Group[30]; 1,626 patients.

TABLE 2.—*Effect of Thrombolytic Therapy on the Global Left Ventricular Ejection Fraction After Myocardial Infarction*

Trial	Agent Administered	Time Delay to Therapy, hours	Patients, No. Treatment/ Control	Method Used to Determine Ejection Fraction	Ejection Fraction Treatment	Ejection Fraction Control	Ejection Fraction Δ	P Value	Date of Assessment, weeks
Western Washington, 1988[13] ...	Streptokinase	<6	191/177	RVG	50.7	47.0	3.7	.08	8
White et al (Auckland), 1987[15] ..	Streptokinase	<4	79/93	Angiography	59.0	53.0	6.0	<.005	3
White et al, 1989[17]	Streptokinase	<3	135	Angiography	58.0	...	...	...	3
White et al, 1989[17]	rt-PA	<3	135	Angiography	58.0	...	...	...	3
Johns Hopkins, 1987[9]	rt-PA	<4	72/66	RVG	53.2	46.4	6.8	<.02	1½
O'Rourke et al, 1988[14]	rt-PA	<2.5	74/71	RVG	52.0	48.0	4.0	.08	3
O'Rourke et al, 1988[14]	rt-PA	<2.5	74/71	Angiography	61.0	54.0	7.0	<.006	3
Australian, 1988[16]	rt-PA	<4	73/71	Angiography	57.7	51.7	6.0	.04	1

rt-PA=recombinant tissue plasminogen activator, RVG=radionuclide ventriculography

The Use of Streptokinase and Recombinant Tissue Plasminogen Activator

Several misunderstandings have contributed to the perpetuation of the controversy concerning the relative merits of using rt-PA versus streptokinase. Originally, both agents were proposed to be equally effective in restoring blood flow during the first 1 to 2 hours following the occurrence of symptoms.[52] This impression was based on an extrapolation of the data generated during the course of the TIMI I trial,[5] however, and there is virtually no evidence to substantiate this conjecture. During the course of this trial, only four patients received either agent within two hours after the onset of chest pain. Among the 28 patients who received thrombolytic therapy within three hours following the onset of chest pain, the recannalization rates for patients given rt-PA and streptokinase were 80% and 44%, respectively.[53] Although there are no reliable data that can be used to compare the thrombolytic potentials of using rt-PA or streptokinase among persons who seek medical attention within two hours of having chest pain, the data generated during both comparative trials and placebo-controlled studies consistently indicate that rt-PA therapy is superior to that of streptokinase in thrombolytic efficacy. Pending any data to the contrary, it is probably inappropriate to assume that the two agents have similar thrombolytic potential when administered within two hours after the start of symptoms.

It has recently been suggested that using streptokinase in combination with aspirin is equivalent to using rt-PA. This conjecture is derived from an interpretation of the ISIS-2 trial[36] mortality data and warrants review. The ISIS-2 trial was a large, multicenter, randomized, placebo-controlled study designed to compare the effects of aspirin, streptokinase, and combined aspirin plus streptokinase therapy on postinfarction mortality. The results indicated that administering aspirin and streptokinase resulted in a 43% reduction in mortality compared with placebo. This was considered comparable to the 46% reduction in mortality reported in the European Cooperative trial,[19] a placebo-controlled rt-PA mortality trial. Because administering aspirin has been shown to confer a profound effect on mortality,[36] this comparison does not provide any useful information concerning the relative efficacy of rt-PA versus streptokinase. Inspection of the data derived from both the ISIS-2 trial and the European Cooperative trial indicates that treatment with rt-PA versus streptokinase resulted in a 46% versus 23% reduction in mortality among comparable treatment and control groups that took aspirin. In short, the data collected to date, including the data from the ISIS-2 trial, have consistently favored the use of rt-PA over streptokinase in reducing postinfarction mortality. Furthermore, it appears that the use of aspirin also enhances the effectiveness of rt-PA (Figure 6).

A third area of confusion concerns the effect of these two agents on the ejection fraction. In general, administering thrombolytic agents results in a modest improvement in the global left ventricular ejection fraction (Table 2). The limited effects of thrombolytic therapy in this regard probably stem from the fact that considerable necrosis commonly develops before recannalization is achieved. In retrospect, it appears that both agents have a similar effect on the ejection fraction (Table 2); however, a recent re-evaluation of the wall motion findings from the TIMI I trial indicated that the regional wall motion was better following the administration of rt-PA versus streptokinase therapy, despite the similarity of the global ejection fractions for both groups of patients.[54] Furthermore, the similarity in global ejection fractions should not be misconstrued to suggest that the two agents are equally useful, as mortality rates have been consistently lower after the administration of rt-PA. One interpretation of these observations is that the prognosis following an acute infarction tends to correlate with coronary patency and not with the ejection fraction.[37]

While rt-PA is consistently more expensive, it is superior to streptokinase in reducing postinfarction mortality. Both agents appear to have a similar effect on the left ventricular ejection fraction and a similar rate of bleeding complications. Given these findings, the controversy surrounding the use of rt-PA versus that of streptokinase can be reduced to a relatively straightforward question: How much will it cost to treat patients with rt-PA versus streptokinase? The data are currently insufficient to answer this question. It is hoped, however, that the results of the GISSI II trial will prove helpful in this regard. This is an ongoing, multicenter trial designed to determine the effects of both rt-PA and streptokinase on postinfarction mortality. The results should be reported in early 1990.

If the results of this trial indicate that the difference in absolute mortality between the rt-PA and streptokinase treatment groups is relatively small, then various other social and financial issues will need to be considered—including the propensity of patients to require additional procedures following the administration of these agents, the frequency with which recipients of these agents return to work, their corresponding productivity, and so forth—to determine the relative cost-effectiveness of the two agents. Of interest is the conclusion from a study in Canada that the use of rt-PA is more cost-effective than that of streptokinase when these

issues are included in determining the relative expense of the two agents.[55]

Although the GISSI II trial will provide some critical data that can be used to determine the relative cost-effectiveness of these two agents, it is likely that a number of economic, social, and ethical issues will need to be considered in order to resolve the controversy that has evolved concerning the relative merits of rt-PA versus streptokinase. Many of these issues are relatively imponderable, and hence it is conceivable that this controversy will continue long after the publication of this trial.

Summary

The management of an acute infarction has changed dramatically over the past 12 years. Although progress has been made, considerable controversy persists. Definitive conclusions must await the completion of ongoing and future trials. There are enough data, however, to permit several conclusions:

- Thrombolytic therapy constitutes the cornerstone of treatment of an acute infarction.
- The efficacy of thrombolytic therapy is critically dependent on the time delay to therapy.
- In recannalizing thrombosed vessels and in reducing mortality, rt-PA is superior to streptokinase. Both agents are similar in terms of impact on the ejection fraction and the incidence of bleeding complications.
- The controversy between rt-PA and streptokinase therapy concerns cost-effectiveness more than biologic efficacy.

Administering a thrombolytic agent alone confers only a modest reduction in postinfarction mortality and infarct size. Hence, these agents should be given in conjunction with adjuvant therapy. Aspirin, β-blockers, and nitrates are among the most promising agents for adjuvant therapy. The data currently do not support doing a routine angioplasty in patients with acute infarction. It is entirely conceivable, however, that data will evolve in support of this approach following the introduction of devices or agents, or both, that effectively prevent the development of reocclusion of the vessel supplying the area of infarction.

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Epitomes

Important Advances in Clinical Medicine

Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Continent Urinary Diversions—Are Appliances Necessary?

DURING THE 1980s many advances have been made in the use of continent urinary diversion for patients with cystectomy. Not only are dry reservoir diversions to the skin becoming available, but more recently internal diversions back to the urethra or to the rectum have become popular. With these advances, cystectomy patients may no longer need to wear an external urostomy bag.

Continent diversions rely on transforming bowel segments into urinary reservoirs with functioning sphincters or valves to prevent reflux and to allow for controlled emptying. While most urologists agree that continent diversions are inherently preferable to those requiring bags, the conduit diversions are still not without advocates. The controversy surrounding continent diversions involves their seeming complexity. Conduits carry with them a track record of more than 30 years of reproducibility and an acceptable rate of short-term complications. More important, the conduit operation can be done safely by most urologists. Continent diversions, on the other hand, are more technically complex and demanding for surgeons and patients alike. The increased operative time required can be accompanied by increased complication rates. The learning curve for surgeons undertaking continent diversion for the first time may be long, which explains why many centers have been slow to adopt this procedure. Where these diversions have been carried out in any number, however, the results have been extremely satisfying. Studies have shown that the quality of life for patients having urinary diversions is enhanced when a continent diversion is employed. A substantial positive difference is noted in these patients in the areas of self-confidence, self-image, physical assuredness, interpersonal relations, and sexual desires compared with those having ileal conduits. With experience, complication rates between the different types of urinary diversions are nearly equivalent. Total continence is not always achieved, and, in our series, 10% to 15% of patients having continent diversions may require surgical revision to achieve an acceptable level of continence.

While continent diversions to the skin have received the most attention, the use of reservoir diversions to the urethra and rectum is being investigated diligently. The concern with internal diversion has been continence. With the method now used to construct diversion reservoirs from detubularized bowel—usually ileum or cecum—extremely low internal pressures can be achieved, allowing for better continence control by the native sphincter mechanisms (external urinary sphincter or anus). Diversions to the urethra are most applicable in men requiring cystectomy who do not have cancer involving the urethra. Rectal diversions with urinary reservoirs may be appropriate in men and women who are not candidates for diversion to the urethra and who do not wish to have a stoma, even a continent one.

In 1989, experience has established that

- Continent diversions, whether to the skin, urethra, or rectum, can replace conduit diversions in most instances;
- Continent diversions are not difficult to construct or maintain;
- Detubularized segments of bowel that are refashioned into reservoirs have improved compliance and provide larger capacities than tubular segments; and
- Patients will demand to be informed about these types of diversions and about the associated quality of life issues.

To benefit fully from these diversions, patients should have the intelligence, maturity, and manual dexterity to care for their own diversions and the life expectancy necessary to resume an active life-style.

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Skinner DG, Lieskovsky G, Boyd SD: Continent urinary diversion. J Urol 1989; 141:1323-1327

Interstitial Cystitis

THE SYMPTOM COMPLEX of urinary frequency and urgency, associated with suprapubic pain, lower back pain, and dyspareunia, commonly occurs in women with urinary tract infection. When these symptoms persist despite antibiotic therapy

and no growth seen on urine cultures, diagnosis and management become more complex. Prominent symptoms of frequency and urgency in association with stress or urge incontinence, especially in an older woman, may be due to either genuine stress incontinence or detrusor instability, which is confirmed urodynamically. Carcinoma in situ should be excluded by cystoscopy and biopsy or urine cytologic examination in older patients, especially men, in the absence of notable bladder outlet obstruction.

Patients with this symptom complex, and after the aforementioned conditions have been excluded, are considered to have hypersensitive bladders. Many of these patients have been given the diagnosis of urethral syndrome, but they all have altered bladder sensation and many may have interstitial cystitis.

Interstitial cystitis is a chronic inflammatory condition almost exclusively found in women. Etiologic research has, in the past, focused on neurologic, endocrinologic, infectious, and psychogenic causes without success. Two theories are now entertained: the possibility that there is a defect in the protective glycosaminoglycan layer of the transitional epithelium, or that interstitial cystitis is a form of autoimmine disease.

The diagnosis depends on the typical symptom complex described, with emphasis on chronicity and associated suprapubic pain. Although cytoscopy done in the office may confirm a painful, hypersensitive bladder, endoscopy should be carried out with the patient under light general anesthesia to fully assess the functional capacity and stretch the bladder to elicit the pathognomonic glomerulations or petechiae. Occasionally a localized fibrotic scar (Hunner's ulcer) may be seen, which has previously been thought to be a cardinal sign of this disease. Cold cup biopsy specimens are taken at this time for histologic evaluation. A pancystitis involving the submucosa and muscularis with a chronic inflammatory infiltrate, edema, hemorrhage, fibrosis, and an increased number of mast cells is characteristically seen. Specific stains are required to count the mast cells, so pathologists should be alerted to get this information.

Treatment is unsatisfactory. Patients with milder symptoms may benefit from bladder drill or other biofeedback techniques that increase the bladder capacity. Bladder distention with the patient under anesthesia is moderately successful and may be repeated if necessary. The use of bladder installations of dimethyl sulfoxide, oxychlorosene sodium (Clorpactin WCS-90), or silver nitrate has enjoyed limited success. Many oral agents have been tried, namely antihistamines and anti-inflammatory drugs including steroids and azathioprine. Recently some response has been ascribed to the use of amitriptyline hydrochloride, the tricyclic antidepressant, and trials continue with sodium pentosanpolysulfate, which theoretically enhances the glycosaminoglycan layer. Subcutaneous heparin can be given for similar reasons, and the use of transcutaneous electrical nerve stimulation (TENS unit) has been advocated by others. Agents such as oxybutynin chloride and phenazopyridine hydrochloride may also be used empirically for symptomatic therapy. Dietary restriction of certain foods including citrus fruits, alcohol, and caffeine may be helpful, as may be alkalinization of the urine with either sodium bicarbonate or potassium citrate.

The surgical treatment of this condition is controversial. If specific ulcers are seen at cystoscopy, they may be resected by electrocautery or laser photoirradiation. Patients who have not responded to any of the conservative measures described may benefit from supratrigonal cystectomy and colocystoplasty. In a recent series, 63% of patients undergoing this procedure were cured of their pain and frequency. More complete excision of the bladder, leaving a tiny cuff of bladder neck for anastomosis, may be considered. As a final resort, urinary diversion may be indicated, and present continent diversion techniques will allow diversion without requiring an external appliance.

Many patients with interstitial cystitis have sought the advice of several physicians before a diagnosis is made. To prevent the inevitable frustration that this induces, this diagnosis should be considered whenever irritative bladder symptoms persist despite simple measures. It is hoped that research directed at etiology and treatment of this perplexing syndrome will provide more effective management.

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Electroejaculation for Recovery of Semen in Neurologically Impaired Men

ELECTROEJACULATION is a technique developed from veterinary medicine that can be used to treat infertility in anejaculatory men. Initially this procedure was used exclusively for patients with spinal cord injuries; more recently, its use has been expanded to include other neurologically impaired groups.

Familiarity with the physiology of ejaculation is important to understanding how this procedure works. Ejaculation is an intricate process that involves emission, antegrade ejaculation, and bladder neck closure. Sympathetic fibers originating from T-12 through L-2 and the thoracolumbar spinal ganglia form the hypogastric nerve. These preganglionic fibers send postganglionic fibers to the prostate, seminal vesicles, and vas deferens. Thus, sympathetic innervation is responsible for seminal emission. Projectile ejaculation, on the other hand, is mediated through parasympathetic innervation.

Electroejaculation, which could more properly be termed electroemission, probably works by stimulating the postsympathetic ganglionic neurons. The procedure involves placing into the rectum a probe that is connected to an electrical stimulator machine. The nerves are then stimulated in a sine wave summation fashion until erection, followed by ejaculation, is produced. Any semen recovered can then be processed and used to artificially inseminate the spouse.

The patients who benefit from this procedure include those men who are anejaculatory following spinal cord injury or retroperitoneal lymph node dissection, or those who have diabetes mellitus, multiple sclerosis, and even psychogenic anejaculation. It is well established that as many as 86% of men who have had spinal cord injury lose the ability to ejaculate and 50% or more of patients who have had retroperitoneal lymph node dissection for testicular cancer do so. There are no figures on the anejaculation rate in men with diabetes mellitus or multiple sclerosis, but certainly this does occur.

Psychogenic anejaculation is fairly uncommon, being estimated to occur in 5% of men.

Using the electroejaculation procedure results in semen obtained sufficient for insemination purposes in about 70% of patients in whom it is attempted. Once it is determined that sufficient viable semen is available, the spouse is evaluated by a reproductive gynecologist. With the use of ovulation-inducing medications and transvaginal ultrasonography, the exact date of ovulation is predicted. On that day, fresh electroejaculated semen is obtained, washed, swum-up, and concentrated. It is then used for high intrauterine insemination. For those specimens that show severely depressed sperm motility or concentration, the electroejaculation process can be combined with in vitro fertilization or, more successfully, zygote intrafallopian transfer. Using these advanced reproductive techniques, the pregnancy rate in our patients is currently 71%, which is substantially better than our earlier rate of 40%.

As with any new technique, a learning curve exists, and complications—most commonly rectal injury—can occur. In experienced hands, however, the complication rate should approach less than 1%. Electroejaculation has provided new hope for this select group of patients formerly considered infertile.

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Management of Ureteral Calculi

THE PASSAGE OF ureteral stones can result in severe pain. The effective advancement of calculi down a ureter requires coaptation of the ureteral walls, and vigorous parenteral hydration will not push the stone down the ureter as by a water nozzle. It is best to keep the patient in a euvolemic state. Most ureteral stones less than 4 mm in size will pass spontaneously. Stones that fail to progress usually get held up at the ureteropelvic junction, where the ureter passes over the iliac vessels, or at the ureterovesical junction. If conservative management is unsuccessful, various interventional options exist.

When stones are located in the distal two thirds of the ureter, retrograde ureteroscopic stone extraction can be done. With such instrumentation, stones can be directly visualized and extracted with baskets or forceps. If a stone is too large, it may be broken into small fragments with an ultrasonic or an electrohydraulic probe or with a pulsed dye laser. Fragments then can be extracted, followed by the placement of a double-J ureteral catheter. With these self-retaining catheters, the proximal J goes in the renal pelvis and the distal J in the bladder. A suture placed at the distal end with enough length to be seen at the end of the urethra allows for a noninvasive extraction.

When located in the upper third, ureteral stones can be mechanically, or with hydrostatic pressure, moved back into a more capacious renal pelvis. In such a position, extracorporeal shock-wave lithotripsy results in excellent fragmentation. In situ therapy is unsuccessful in as many as 30% of patients, with failure related to the stone size, composition (especially calcium oxalate monohydrate and cystine), and degree of impaction, some of which are unknown preoperatively. As the stone burden increases, the volume of stone gravel also increases and, at times, can result in an accumulation of gravel in the ureter resulting in *steinstrasse* (stone street). In the hopes of preventing such complications, a double-J catheter is placed for all stones greater than 1.5 cm.

Large proximal ureteral stones may be approached in an antegrade manner through a percutaneous nephrostomy tract. The need for open surgical extraction is, indeed, rare in the modern era of endourologic instrumentation. Ureteral stones can cause severe anguish, both for patients and physicians. The varied therapeutic options in dealing with such stones have revolutionized our approach.

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Nerve-Sparing Radical Prostatectomy

IN THE PAST 20 YEARS, the treatment of potentially curable, localized prostate cancer has emphasized preserving the quality of life and, at the same time, attempting to control if not eradicate the primary tumor. Examples of these trends include the uses of external beam irradiation and brachytherapy—the implantation of interstitial irradiation—in an attempt to preserve potency. On the other hand, the standard radical prostatectomy, when carried out in patients without risk factors, such as a previous prostatic operation, irradiation, or both, has offered an acceptable degree of perfect to excellent urinary control at nearly 95%. A staging pelvic lymphadenectomy is recommended to define patient curability before any therapeutic approach is taken.

With the dissemination of information on the neurovascular anatomy of the prostate and how urologists may be able to do adequate radical (total) prostatectomy with the preservation of at least one neurovascular bundle to sustain potency, interest in the surgical treatment of localized disease has again increased. Research on the technique of nerve-sparing radical retropubic prostatectomy has more recently been applied to perineal prostatectomy for localized disease. Thus, the advantages of the perineal route—improved vascular control, direct vesicourethral anastomosis, and the like—can be combined with sparing of the neurovascular bundle(s) to maintain potency.

Substantial risk factors that militate against preserving potency include older age and extensive prostatic and extraprostatic disease. Thus, the ideal patient for a nerve-sparing prostatectomy, either retropubic or perineal, is a potent man younger than 65 years who has low-volume (low-stage), low-grade prostatic cancer. The maintenance of potency in this patient group has been reported as high as 75% to 80%, with some men being able to achieve satisfactory erections immediately after the operation. On the other hand, erectile function has not returned until 12 to 18 months following the operation in some men, likely reflecting neuropraxis. Conversely, in patients older than 70 with extensive intraprostatic

cancer, the chance of maintaining potency postoperatively is only about 10%.

Surgical technical points include dividing the lateral prostatic pedicles close to the prostate at least on the side opposite to the known tumor, sacrificing the neurovascular bundle, if necessary, on the side of tumor to encompass the disease, carefully dissecting the membranous urethra to prevent injury to the cavernous nerves, and using a vertical rather than a transverse division of Denonvilliers's (ventral rectal) fascia for perineal exposure.

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Transrectal Ultrasonography of the Prostate

PROSTATIC ADENOCARCINOMA is currently the second most common male cancer and the second leading cause of cancer deaths. Despite advances in the treatment of localized cancer of the prostate, including improvements in surgical techniques with resulting decreased morbidity and novel approaches to radiation therapy, only about 50% of men have clinically localized disease amenable to such approaches. Transrectal ultrasonography offers the best method for imaging the prostate and has many applications in the management of this ubiquitous neoplasm.

Despite its introduction several years ago, transrectal ultrasonography has only recently received widespread investigation and clinical acceptance. Technical advances that have resulted in excellent imaging include the observation that transducers in the 6- to 7-MHz range offer the optimum balance between lesion resolution and organ penetration, and the development of probes that allow imaging of the prostate in the axial and sagittal planes (biplanar). It is now widely accepted that on transrectal ultrasonography most carcinomas appear as hypoechoic lesions in the peripheral zone (adjacent to the rectal surface) of the prostate.

The transrectal ultrasound examination (and biopsy) is most often done in a clinician's office and requires no anesthetic. We recommend giving a Fleet's enema before the procedure and, if a biopsy is anticipated, routinely administering an aminoglycoside or oral quinoline. With the patient in the lateral decubitus position, a 2- to 3-cm diameter probe is inserted in the rectum, and images are taken from the base of the bladder to the apex of the prostate in the axial and sagittal planes.

Transrectal biopsy of suggestive lesions is readily done without the use of anesthesia, using a spring-loaded gun that, combined with a biopsy needle, obtains excellent tissue cores. This instrument is placed through a biopsy guide on the prostate probe and, under ultrasound guidance, the needle is placed within the lesion and a specimen taken. It must be noted that a number of noncancerous lesions have a sonographic appearance indistinguishable from carcinoma. These include benign hyperplasia, acute and chronic inflammation, atrophy, skeletal muscle, and prostatic intraepithelial neoplasia (a putative premalignant lesion). In our experience with more than 400 such biopsies, 35% reveal carcinoma.

Although biopsy guidance may be the greatest use of transrectal ultrasonography, other applications include the staging of an established malignant tumor, monitoring of radiation or androgen ablation therapy, and the early detection of adenocarcinoma. The issue of screening has generated considerable attention. The combination of transurethral ultrasonography and prostate-specific antigen may allow the identification of even a greater number of cases of prostate cancer. In this neoplasm, where the pathologic incidence far exceeds the clinically manifested disease, the appropriateness of screening is controversial. A prospective, randomized clinical trial is mandatory to determine the effectiveness of ultrasonography not only for detecting carcinoma but, more important, for improving the rates of patient morbidity and mortality.

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Newborn Circumcision Controversy

FEW TOPICS engender as much controversy as that of newborn circumcision. In 1975 the American Academy of Pediatrics (AAP) suggested that "there is no absolute medical need for routine circumcision of the newborn." In 1970 almost 90% of newborn boys in the United States were circumcised and, probably because of this change in attitude from the AAP, by 1988 it was estimated that the percentage had fallen to about 60%. Organizations such as the National Organization of Circumcision Information Resource Centers (NOCIRC) became active in outlining reasons to end routine newborn circumcision. These included saving the protective role of the foreskin, decreasing the risks and complications of the procedure, eliminating pain from the circumcision, and obviating the reputed long-term psychological effects and purported sexual dysfunction. Finally, they raised questions as to the ethical and legal issues raised by operating on a nonconsenting infant.

In 1975 a decreased incidence of urinary tract infections was described in circumcised male infants when compared with uncircumcised infants, and then again in 1986, evidence was outlined for the decreased incidence of urinary tract infections in circumcised male infants. A tenfold increase in the incidence of urinary tract infections was found in noncircumcised compared with circumcised infants, and because of these data, it was suggested that there was at least one medical benefit for the practice of routine, neonatal circumcision. Because of these findings, a new task force on circumcision of the American Academy of Pediatrics was formed and the report released in April 1989. The report suggested that properly done newborn circumcision prevents phimosis, paraphimosis, and balanoposthitis and has been shown to decrease the incidence of cancer of the penis. Further, it

stated that "it may result in a decreased incidence of urinary tract infections" and that "evidence concerning the association of sexually transmitted disease and circumcision is conflicting."

In summary, the AAP suggested, in contradistinction to its 1975 position, that newborn circumcision has potential medical benefits and advantages as well as disadvantages and risks, and that benefits and risks should be explained to the parents and informed consent obtained. Although the final word has not been written about this controversial and provocative topic, further studies may be needed to answer many questions as to its efficacy and desirability.

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Urologic Care of Children With Myelodysplasia

IN THE PAST 10 YEARS many changes have occurred in the care of children with myelodysplasia, mirroring the increased understanding of the functional abnormalities in the lower urinary tract. The use of diapers or supravesical diversion is no longer acceptable, as in most cases, continence is readily achievable. Urodynamics have shown that incontinence in these patients is due to an abnormally increased bladder pressure—poor compliance, hyperreflexia, or a combination of both—and inefficient emptying, associated with a bladder outlet that has a fixed resistance and is unable to respond to changes in abdominal or detrusor pressure. The upper urinary tract is sensitive to an abnormally increased bladder pressure, producing vesicoureteral reflux, hydronephrosis, and, eventually, renal deterioration.

This vesicourethral dysfunction is easily evaluated in the neonatal period urodynamically, identifying those cases of possible upper tract deterioration. Early intermittent catheterization along with the administration of anticholinergic medication, such as oxybutynin chloride, has been shown to prevent these changes and reverse reflux or hydronephrosis if present. About 10% of infants will require this early intervention, and no problems have been encountered with this form of management. Difficulty catheterizing an infant or further renal deterioration occurring despite these conservative measures should be a strong indication for vesicostomy.

Most children will simply be followed up on a regular basis with renal ultrasonography and urine cultures. Attempts to achieve continence will be made, assuming there is no further renal deterioration, at around 3 to 4 years of age. Intermittent catheterization and the use of anticholinergic medication are the mainstays of treatment. The use of imipramine hydrochloride, ephedrine, or both is occasionally required for satisfactory continence. More than 80% of myelodysplastic children can achieve continence in this way. For those who remain incontinent, surgical intervention is required. The bladder outlet may be enhanced by a compressive fascial sling, or an artificial sphincter may be implanted. These procedures need to be combined with an augmentation cystoplasty to reduce the bladder pressure and allow appropriate urinary storage. These reconstructive techniques may also be used in those myelodysplastic patients who have had a previous diversion and have become unhappy with, or have problems with, their stoma or external appliance (undiversion). Some patients, often chairbound girls, may require some form of supravesical diversion. Satisfactory results have always been difficult in these patients because of their body habitus, but a continent catheterizable urinary reservoir can now be constructed so that an external appliance is no longer necessary.

Another technique that shows promise for the future is intravesical electrical stimulation; increased bladder control has been achieved with this intensive therapy.

Using these techniques, the prospects for urinary continence and normal renal function are now excellent in most children born with a myelomeningocele deformity.

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Editorials

A Watershed Moment for World Health?

AT THE RECENT ECONOMIC SUMMIT in Paris, the environment seemed to begin to come of age on the world agenda. It was a landmark for environmental health when the leaders of the seven Western nations agreed that the time has come to recognize the relationship of a healthy world environment to human health and, by the same token, to economic health and prosperity. This is a welcome pronouncement of commendable intent, but one senses that it may be some time before there is agreement and action on what needs to be done, how it will be done, and when or by whom. Governments—that is, the public sector of society—tend to think and work more for the present than for the future. The same can be said of the private or business sector. Experience to date shows that neither will venture easily into what will be long-range and no doubt costly preparations to ensure a healthy environment for a healthy future, since there is unlikely to be an immediately measurable payoff. The stimulus will need to come from elsewhere, and it will need somehow to be broadly based throughout the world.

There are some precedents, however. For example, environmental groups and organizations have been able to bring about change and long-range action in both the public and private sectors of society, particularly in the United States. Physicians have been active in these groups, often playing leading roles. And it is probably fair to say that physicians, through organizations such as the International Physicians to Prevent Nuclear War, have had some influence on an international scale to protect the health of present and future generations. After all, this organization won the Nobel Peace Prize in 1985. It is also worth noting that there is a professional bond among physicians that extends well beyond national boundaries. Physicians, wherever they are, have similar professional backgrounds and individually and through their organizations share a deep professional and humanitarian interest in human health and well-being.

Society looks to the medical profession for authoritative guidance in matters pertaining to health. The profession is charged with providing the knowledge and skills needed to diagnose, treat, and prevent illness, and to promote health. The relationship of the human environment to personal illness can be close, and physicians see the effects of this relationship in their everyday practice, including the obviously harmful effects of pollutants of land, sea, and air on their patients and the public.

If there is ever to be effective action on a community, state, national, or international scale to assure a healthy environment and a healthy world for humanity, it would seem that there is an opportunity and even an obligation for physicians everywhere to come forward and provide the stimulus that will help to bring this about. It is not likely that this will arise from within the established power structures, where the tendency is always to be preoccupied with matters of the moment. One could almost say that it is a professional duty for physicians, individually and collectively, to at least stimulate the needed stimulus. This will require physician visibility and persistence that will be in patients' and the public's interest, and this should not hurt but rather enhance the public's opinion and image of our profession. And it could lead to a watershed moment for world health.

MSMW

Anticoagulation—'Sufficient Conclusions From Insufficient Premises'?

THE THESIS that coumarin compounds would have antithrombotic efficacy was founded on the observations that the oral anticoagulants produced both a bleeding disease in cattle and a few seconds' prolongation of a test tube assay designed to recognize hemophilia. Today hypotheses based on such evidence alone would be unlikely to reach the state of clinical trial. Yet, clinical trials, such as they were more than 40 years ago, convinced many clinicians that the coumarins were broadly effective antithrombotic agents. The use of oral anticoagulants, widespread in the treatment of myocardial infarction by the 1950s, reached a nadir in the following decade. During the 1970s and 1980s, however, anticoagulant prophylaxis began a gradual climb to a more limited acceptance. Stults and colleagues elsewhere in this issue have chronicled the anticoagulant story with unusual objectivity. What is additionally striking about their detailed and meticulous reporting is that all but 20 of their 175 references come from the present decade—strong evidence of the extent of recent efforts to restore these agents to a more prominent role in the growing menu of antithrombotic drugs.

Where clinical trial data do not yet provide easy answers, however, it is possible to suggest interim clinical options. For example, there is a broad consensus that anticoagulant therapy diminishes the recurrence rate of venous and systemic thromboembolism among patients postoperatively and those with acute myocardial infarction, atrial fibrillation with organic heart disease, rheumatic valvular heart disease, prosthetic heart valves, and idiopathic dilated cardiomyopathies (group I). In contrast, evidence that anticoagulants are of value in the management of old myocardial infarction, transient ischemic attacks, and postcerebral infarction states (group II) does not attain a comparable level of consensus. What this dichotomy recalls is that, while all thrombi in humans are mixed, some clearly have a predominantly fibrin component, whereas others consist largely of platelet aggregates. Animal models and clinical trials make clear that it is against the former type of thrombus (group I) that oral anticoagulant therapy is particularly effective. Those conditions in which benefit from the coumarin derivatives appears less convincing (group II) or, in the view of some investigators, are preferably managed by other antithrombotic agents tend to have platelet aggregates predominate. But when, as in crescendo angina, fibrin and platelets are variably mixed, administering aspirin and heparin separately has provided favorable outcomes. Ongoing and proposed clinical trials with a broad range of antithrombotic agents and regimens, alone or in combination, may define better the therapeutic choices for patients with crescendo angina.

The question next arises as to what are the most appropriate anticoagulant schedules for prophylaxis among group I and group II patients. These regimens can be defined, for

warfarin, somewhat arbitrarily in terms of prothrombin time (PT) ratios using United States thromboplastins as follows: ultra-low dose: PT ratio of 1.2 and below; low dose: PT ratio of 1.3 to 1.7; medium dose: PT ratio of 1.6 to 1.9; and high dose: PT ratio of 1.8 to 2.1. The use of ultra-low-dose warfarin—with or without low-dose aspirin—cannot be justified as the long-term clinical efficacy has not yet been established. Contrariwise, high-dose regimens cannot be accepted as the long-term risks of hemorrhage are excessive. The options, in this view, are reduced to the choice between low- and medium-dose prophylaxis that overlaps slightly.

There is no longer any question that recurrent venous thromboembolism can be prevented at the low-dose range. Whether arterial thromboembolism would be equally well contained by that regimen among group I patients, while reasonable from the pathologic viewpoint, has not yet been confirmed by adequate clinical trial. One further clinical observation, stated originally in 1950,[1] needs reemphasis: namely, that greater intensities of anticoagulant therapy are required immediately after the onset of an acute thrombotic process than are necessary to prevent recurrences.[2]

Support for some of the views expressed here comes from clinical trials reported since the manuscript by Stults and co-workers was accepted for publication.[2-4] Moreover, after considering the variables inherent in the prothrombin time assay itself, in the many features that may promote bleeding, in the knowledge that administration may involve a lifetime of use, and that many of the patients most needing long-term prophylaxis are in their 70s and 80s, it would appear reasonable to suggest that a majority of the group I patients at risk of systemic embolism can probably be managed at the low-dose ratios. In deciding on low- or medium-dose warfarin regimens, one must appreciate that the terms "low-risk" and "high-risk" patients depend both on the accumulated risk factors that a patient brings to the present illness and on the degree of thrombogenicity induced by the illness itself. For patients in whom the combined risk factors add up to a low or medium risk, a low-dose regimen may be adequate. For high-risk patients, the medium-dose range may be necessary. The latter can be justified so long as both physician and patient appreciate that a greater risk of bleeding is incurred.

Group II patients present a greater challenge in the selection of PT ratios. It would be consistent with the view already expressed that group II patients should be considered for medium-dose prophylaxis with all the caveats that such a choice implies. If the latter fails—as will inevitably occur with any antithrombotic agent—a modality other than warfarin should be considered rather than commit a patient, long term, to the hemorrhagic risks of a high-dose regimen. This is particularly true among patients with cardiac and cerebrovascular disease in whom life-threatening thromboembolic events are uncommon or in whom the anticipated benefit of anticoagulation is modest.

Considering the state of the art, the indications for prophylaxis detailed earlier should be construed as suggestions rather than mandates, since they do not all represent a broad consensus and will undoubtedly undergo modifications with time. The difficulty in advising physicians as to which conditions and at what intensity anticoagulation should be employed today is best epitomized by the English novelist Samuel Butler's 1912 view: "Life is the art of drawing sufficient conclusions from insufficient premises."[5(p11)]

In regard to the prothrombin time itself, there are practical recommendations concerning the performance of the assay per se as well as the manner in which the results are reported that can influence favorably the precision with which warfarin is administered. Organizations responsible for the approval of clinical laboratories should require that blood specimens for prothrombin times be collected in what are classified as "clinical grade," polymer-lined tubes such as polypropylene and *not* in glass or imperfectly siliconized glass vessels. The availability of a "clean" polymer vacuum tube containing sodium citrate would facilitate the practicality of this recommendation. The artifactual shortening of the prothrombin time when blood is collected in glass or imperfectly siliconized glass tubes begins within an hour, is pronounced within two to four hours after venipuncture, and can readily lead to drug overdose.[6] Clinical laboratories are also remiss if they do not at least report their control values with each patient's prothrombin time. In addition, the ratio of a patient's prothrombin time to the control value should be provided, for that is the actual piece of information on which dosage is based. Clinical laboratory resistance to these recommendations must reckon with the reality that, for the foreseeable future, a prothrombin time will remain the effective means of regulating the dose of warfarin—the drug of choice for thousands of patients at risk of pulmonary and systemic thromboemboli.

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Alcohol and the Cardiovascular System

In this issue of the Journal, Davidson has extensively reviewed the multiple effects that ethyl alcohol may have on the cardiovascular system, which may be either harmful or potentially beneficial. Among the harmful effects is the capacity of ethanol to induce heart failure when chronically abused. As a separate phenomenon, the effects on cardiac conduction and rhythm are analyzed. Of particular note is the increased risk of sudden death in heavy drinkers. The epidemiologic evidence linking alcohol to hypertension and stroke and its putative preventive role in coronary artery disease are examined. It is noteworthy that the variability of the target organ affected by chronic alcoholism implies a difference in genetic susceptibility of cells that renders individual tissue prone to ethanol toxicity.

Davidson elaborates several weaknesses in the linkage of modest ethanol use to a reduction of coronary artery disease manifestations. Factors other than the moderate use of ethanol may be implicated. Patients in this subset tend to have lower basal arterial pressure and body weight.[1] Further-

more, they appear to have a lower intake of total saturated fat and a higher intake of polyunsaturated fatty acids.[2] A persistent flaw has been the composition of the control group. It is believed that there are sufficient ex-drinkers in this group to compromise its validity, since they share a number of characteristics that increase their cardiovascular risk. These include a higher prevalence of cigarette smoking, obesity, and hypertension compared with those who were never drinkers.[1] Moreover, they are likely to be unmarried and to work in manual occupations. In the final analysis, if modest alcohol ingestion proves to have a preventive effect, its usefulness as a general public health measure would be limited by potential addictive consequences.

At the other end of the population spectrum, the effect of substantial use may be underestimated by the nonparticipation of heavy drinkers in large-scale studies. Their identification adds significantly to this field because they are at increased cardiac risk.[3]

In terms of heart failure and its prevalence in the alcohol-abusing population, this is difficult to determine because of the methodologic difficulties discussed by Davidson. When considered in relation to other forms of congestive cardiomyopathy, ethanol use has been found to be the etiologic factor at a range between 21% and 32% of cases.[3] The assumption that the incidence may be higher at institutions that serve a population with a relatively high incidence of alcoholism appears reasonable.[4]

A variety of studies support the belief that there is a relatively long gestational period before the clinical appearance of cardiac disease, analogous to that of liver disease. Most studies examining addicted persons without clinical evidence of heart disease find an incidence of subclinical abnormalities approximating 50% by noninvasive testing.[5] In middle-aged men who have been drinking heavily for ten years or more, an echocardiogram may reveal an increased thickness of the interventricular septum and posterior left ventricular wall without an abnormality of the ejection fraction or chamber diameters. That the earliest abnormalities are related to diminished compliance has been supported by the finding of a notable increase of the end-diastolic pressure with a slight reduction of the end-diastolic volume.[5] Moreover, contractile velocity indices are diminished at this stage when the ejection fraction may not be substantially abnormal. There is suggestive evidence that when a patient becomes abstinent at this stage of the disease, the process may be reversed. Certainty on this point, however, requires larger scale, long-term studies.

Cardiac decompensation typically occurs in men between 30 and 55 years of age who have ingested at least 80 grams of alcohol on most days for at least ten years. When left ventricular dysfunction progresses to low-output heart failure, exertional or nocturnal dyspnea occurs. Weakness and fatigue may be prominent complaints. Physical signs of cardiac decompensation are similar to those observed with other forms of congestive cardiomyopathy.

Cardiomegaly may be due to the primary myocardial process or to mitral regurgitation related to papillary muscle insufficiency. An associated apical murmur is characteristically confined to a portion of systole and as a rule changes as cardiac compensation is restored. Because an addicted person may frequently delay seeking medical assistance for weeks to months, evidence of right-sided heart failure is not uncommon, with distended jugular veins, an enlarged tender liver, and edema of the dependent portions of the body. This may be erroneously identified as primary right-sided heart failure.

It is noteworthy that even before this stage, the presence of poor R wave progression on a precordial electrocardiogram may suggest coronary artery disease. Coronary angiography, however, usually reveals normal vessels.

A variety of atrial dysrhythmias have been described in patients without overt cardiomyopathy or enlarged hearts. Acute intoxication is typically superimposed on a background of alcoholism. Characteristically atrial fibrillation is the most common arrhythmia, and plasma electrolytes are usually normal. Sinus rhythm may be restored spontaneously in some but usually requires cardioversion or pharmacologic intervention. After a normal sinus rhythm was restored, moderate conduction delays were found on a high-speed electrocardiogram and were considered to be the background for the induction of acute arrhythmias.[6]

Moreover, in an analysis of new-onset atrial fibrillation in 40 patients younger than 65 years, alcohol use was considered to be causative or contributory in approximately two thirds.[7] This phenomenon has been reproduced in electrophysiology laboratories.

In view of these observations, it is surprising that evidence of ventricular tachycardia in these patients is sparse. One explanation could be that ventricular tachycardia in alcoholic patients rapidly progresses to fibrillation before medical assistance. Although several reports from medical examiners in this country have indicated a high incidence of sudden death in persons who abuse ethanol, this issue has been more fully delineated in a prospective study of sudden death at the Pathology Institute in Moscow. The authors revealed that 17% of these deaths were related to alcohol abuse, and these were predominantly in patients younger than 50.[8] None could be attributable to sleep apnea; inclusion in the study required that the event be witnessed and that death occur within 30 minutes of symptoms. Significant coronary artery disease was absent in these patients, but evidence of cardiomyopathy by light and electron microscopy was present in specimens taken within hours of death.

Although social drinking is often associated with a small rise of the systolic arterial pressure, persons who habitually imbibe heavily often show rises of systolic and diastolic pressure that may be substantial. These hypertensive responses are not related to a high-output state, since peripheral arterial resistance is substantially increased.[9] Transient pressure elevations in nonalcoholic persons are not considered to give rise to myocardial disease, and in an addicted person this transient hypertensive state is commonly unassociated with clinically significant heart disease. As indicated, it is hoped that this issue will soon be clarified.

Whether fixed hypertension can develop in persons who have frequent vasoconstrictive responses to ethanol withdrawal is not clear. Studies of cardiac function in alcoholic patients, when carried out days to weeks after the last ethanol consumption, have shown normal arterial pressure in the preclinical state, mild heart failure, or failure after compensation.[3] Moreover, in none of these studies were such consequences of hypertension as retinopathy reported.

Epidemiologic studies have indicated a positive association between the amount of alcohol consumed and the development of cerebrovascular accidents. This relationship is most notable in patients younger than 50 years and includes

hemorrhagic and nonhemorrhagic events.[10] The former were even found in middle-aged women who consumed moderate amounts.

Although this phenomenon has been reported to be independent of blood pressure readings, a transient pressure elevation before and during a stroke has not been excluded. More important, patients who reduce their alcohol intake apparently have a considerably lower risk of hemorrhagic stroke developing than those who maintain their usual intake, but additional prospective studies are required to confirm this observation.

In all of the syndromes mentioned earlier, an accurate history of alcohol abuse may not be readily obtained. Alterations in the composition of blood may aid in the diagnosis. The mean corpuscular volume of the red cell may be increased as well as liver enzyme concentrations. The γ-glutamyl transferase measurement appears particularly useful. Albumin and urea levels may be reduced and high-density lipoprotein and transferrin concentrations enhanced. While not available currently in routine clinical laboratories, an analysis of platelet membranes may be particularly useful. Membrane activity of monoamine oxidase and adenylate cyclase, while normal in the basal state, shows reduced responses to biochemical stimulations that appear to persist for months to years after abstinence is begun.[11]

Although endomyocardial biopsy has not been particularly useful, skeletal muscle is a readily available tissue for biopsy in identifying alcoholism. Atrophy of striated muscle fibers has been reported particularly of type IIB fibers, which is a relatively specific finding.[12]

The salient feature of long-term management for all of the cardiovascular consequences of alcoholism is abstinence, which has been associated with a decline in the incidence of stroke and hypertension. On the basis of a four-year follow-up study of patients presenting with cardiac decompensation, this also appears to apply to the myocardial complications. A third were found to have apparently maintained abstinence, and the majority of these had an improved or unchanged cardiac status, with a 9% mortality.[13] Because 20% of those who were allegedly abstinent deteriorated in cardiac status, at certain stages of the disease the pathogenetic mechanisms may continue unabated. More than half of those who remained actively alcoholic died.

Heart failure is traditionally managed medically, and treatment is guided by the severity of the process. In view of the high incidence of mural thrombi, anticoagulation can be used if the coagulation system is relatively normal and the patient is currently abstinent. When a patient is actively alcoholic, this therapy should not be applied. It should be noted that in this circumstance, therapy for those with chronic essential hypertension is also relatively ineffective.

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Special Editorial

UCSF—An Academic Health Science Center at 125 Years of Age

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THIS MONTH the University of California, San Francisco (UCSF), will begin a year-long celebration of its 125th birthday. From its somewhat raffish beginnings in 1864 as the proprietary Toland Medical College—four years before the founding of the University of California itself—it has slowly grown into a modern academic health science center. This center, which now also embraces schools of Dentistry, Nursing, and Pharmacy, as well as a Graduate School of Biomedical Sciences, is the largest nongovernmental employer in San Francisco. More important, it is a major international center for professional education and continuing education, for patient care, and for biomedical research. In addition, beyond its central academic functions and its economic impact, UCSF offers a remarkable array of community services, from outreach clinics to imaginative approaches for improving the teaching of sciences in the public schools of San Francisco. It is therefore simultaneously an integral part of the fabric of its community and a major participant in the general advances in biomedical science and technology and in the application of those advances for the prevention and alleviation of human suffering.

With some variations in longevity and in the composition of their constituent schools, this description could be applied equally as well to all academic health science centers in the purview of *The Western Journal of Medicine.* There is a unique relationship of a university to medical education that is well known but rarely discussed: it is only in medicine that a university is directly engaged in a major industry—or societal activity, if you prefer—other than that of education itself. The law schools teach law, but they do not administer justice; the business schools teach economics and management, but they do not operate businesses; engineering schools are not engaged directly in construction. The list could be continued, since by tradition universities create and transmit knowledge, but they are not directly engaged in its application in the world beyond the groves of academe. Not so in medicine. Here, there is no sharp discontinuity between the margins of the university and the industry of health care, and it is through the academic health science center that this uneasy linkage is effected. When the practice of medicine is buffeted by social and economic forces, the academic health science centers, and medical education itself, share with the profession at large the consequences that follow. Academic medicine is not, therefore, "the leisure of the theory class," as one perverse inversion would have it. It must constantly adapt if it is to remain both relevant to modern medicine and economically viable.

The general public can readily understand the central role of the academic health science centers in educating the future generations of skilled professionals in all fields relating to health. Even more compelling to the average citizen is the direct role of a university such as UCSF in rendering patient care through its own teaching hospitals and clinics (the Moffitt-Long Hospital) and through those that work in close academic partnership with it (the San Francisco General Hospital Medical Center, the San Francisco Veterans Administration Medical Center, Mount Zion Hospital and Medical Center, and many others). The public is rarely aware of the range of community services that such academic health science centers offer or of the remarkable economic and social influence that they have in their respective communities (for UCSF, an annual budget of almost $700 million and a work force of approximately 13,000, of whom 35% are underrepresented minorities). More ambiguous is the public's response to research, at least as reflected in many of its most strident voices.

It can be argued that the main problem in health care in our time is not its cost or its inequitable and often unjust distribution, serious as these problems undoubtedly are. It lies in the continued existence of diseases for which we have no answers—or for which we have, in Lewis Thomas's phrase, only a "halfway technology" rather than a final answer: in the past, iron lungs rather than a polio vaccine; in the present, angioplasty rather than an effective control of atherogenesis. Even if the most advanced medical science and technology were universally available, patients would still die prematurely of heart disease, cancer, and AIDS and would still become insane from schizophrenia or crippled from rheumatoid arthritis. The only rational policy, therefore, is a form of national defense in the support of basic and applied biomedical research—not Star Wars against a hypothetic enemy, but Terrestrial Wars against inevitable individual disability and death. The academic health science centers are in the vanguard of this rewarding national strategy.

In support of "defense" through biomedical research, the federal government spends about $30 annually for each American citizen; in support of more traditional forms of military defense, it spends approximately $1,200 annually for each citizen. The effort in biomedical research, relatively small as it is in context, is still capable of arousing antagonism from a collection of unlikely confederates: the more extreme factions for animal rights; the neo-Luddites who reflexively fear all scientific advances; the neo-Chernobylites or Bhopalites who pander fears that the use of isotopes and "toxic chemicals" in medical research endangers the surrounding community despite the absence of any evidence that this is so; and the professional contras who tend to oppose all institutional growth and development. Such alliances have hindered the expansion of biomedical research at UCSF, at Stanford, and at Berkeley and will undoubtedly be an increasing deterrent to medical progress in all settings in the future. Academic health science centers, and, indeed, the profession of medicine at large, must take these challenges

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seriously and jointly accept the responsibility to educate the American people about the vital stake that they have in biomedical research if rapid progress is to be sustained.

From a small, informal "medical school" organized and even owned by Doctor Hugh Toland in post Gold Rush San Francisco to the large, complex academic health science center that is UCSF today, the stretch of 125 years has brought remarkable changes in size and scope. But, as Groucho Marx lamented, "Even the future isn't what it once was." The academic health science center—be it UCSF, the University of Colorado Medical Center, UCLA, the University of Arizona Medical Center, or any of the approximately 15 such centers in the West, or indeed any of the approximately 130 such centers in the United States—will face new challenges in the immediate years ahead as we rapidly approach the 21st century. Will they be able to maintain balanced programs in education, patient care, research, and community service during the turbulence that lies ahead? Will they continue as vital links between the university and the profession? Will they offer leadership for or be drawn passively into the changes that will occur in our national system of health care? While we properly celebrate past achievements, these questions remain to fret and erode our complacency.

The University of California, San Francisco, Medical Center photographed in the 1970s (not pictured, the School of Dentistry building). Courtesy of Steve Proehl.

Case Reports

'Yewdow'-Induced Anemia

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GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) deficiency is a common cause of a sudden unexpected anemic crisis. It is often difficult to trace the exact inciting agent for the hemolytic episode. We report a case of life-threatening hemolytic anemia in a healthy Chinese-Burmese boy who had never been ill to underscore the problem posed by this clinical conundrum.

Report of a Case

The patient, a 2½-year-old boy, had a sudden onset of dark red urine, pallor, and decreased appetite after spending the night with his grandparents. The child had had no previous upper respiratory tract infections, fever, diarrhea, epistaxis, or jaundice. His parents said he had not had exposure to pesticides, prescribed drugs, ethnic herbal medications, teas, or fava beans. The neonatal history was unremarkable for any jaundice, phototherapy, or sudden pallor. Both parents worked in a sewing factory and did not bring their work home.

The child was well developed and pale, with a blood pressure of 107/47 mm of mercury, a pulse rate of 104 beats per minute, and tachypnea with respirations of 40 per minute. Pertinent findings included an intermittent grade I/VI systolic murmur at the left sternal border, poor capillary filling in all extremities, and no organomegaly. He had no petechiae, ecchymoses, or rashes. The hemoglobin concentration was 2.54 mmol per liter (4.1 grams per dl), hematocrit was 0.11 (11%), and the mean corpuscular volume was 102 fl. The uncorrected reticulocyte count (brilliant cresyl blue wet mount) was 68×10^{-3} (6.8%; normal, 1 to 24×10^{-3}), and numerous Heinz bodies were found. A peripheral blood smear revealed moderate anisocytosis and poikilocytosis with fragmented erythrocytes seen. There was pronounced hemoglobinuria, proteinuria, and bilirubinemia. The blood urea nitrogen level was 8.9 mmol per liter of urea (25 mg per dl; normal, 3.0 to 6.5), the serum creatinine was 90 μmol per liter (1.0 mg per dl; normal, 50 to 110), total serum bilirubin was 112 μmol per liter (6.6 mg per dl; normal, 2 to 18) with 5 μmol per liter (0.3 mg per dl) direct-acting bilirubin, alanine aminotransferase was 23 U per liter, aspartate aminotransferase was 98 U per liter, and lactic dehydrogenase was 1,479 U per liter. Serum tests for antibodies to hepatitis A and B, heterophil agglutination, and Coombs' testing were negative. Emergency therapy consisted of transfusion with packed red cells and mannitol- and furosemide-induced diuresis. The patient recovered completely in four days, with a return to normal of his blood chemistry values.

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Figure 1.—Several fried fava beans (*Vicia faba* Leguminosae; "yewdow") are shown.

Several months later, the patient was shown to have 0 IU of G6PD enzyme activity per gram of hemoglobin (normal range, 7.9 to 16.3 IU per gram). His hemoglobin at that time was 7.57 mmol per liter (12.2 grams per dl), and his reticulocyte count was 24×10^{-3} (2.4%). Both parents had some G6PD activity detected on a spot test. The parents were again questioned (by a Chinese physician [W.Y.W.]) as to possible ingestions and exposures. The physician asked about "yewdow" ingestion and learned that the child had eaten a packet of this common Asian snack food while watching television with his grandfather. "Yewdow nuts" are prepared from the seed pods of the *Vicia faba* Leguminosae plant, which is the identical species of Mediterranean fava (broad) beans.

Discussion

Glucose-6-phosphate dehydrogenase deficiency is found in persons throughout the world, but is more frequently reported from the tropics and Mediterranean areas. There are more than 150 variants of the G6PD enzyme. The A− variant is found more commonly in blacks. G6PD B− and G6PD Canton are found in populations of the Mediterranean and Southeast Asian regions. Both increased spectrin and decreased glomerular-stimulating hormone levels have been implicated in the mechanism of erythrocyte damage.[1] The selective advantage of G6PD deficiency in malaria-endemic areas was suggested by Allison[2] and Motulsky[3] in the 1960s and further substantiated by Usanga and Luzzatto[4] in the 1980s. This enzyme deficiency has been found to confer an additional antimalarial advantage,[5] but this advantage disappears when a patient is transplanted to an area nonendemic for malaria. Panich has determined the frequency of G6PD deficiency in several Asiatic populations.[6] Of particular importance to physicians in California is the fact that 5% of Southeast Asian male refugees to the United States had decreased G6PD activity.[7]

Incriminated agents inducing hemolysis include the well-known sulfonamides and antimalarial drugs, nitrofurantoin, infections such as hepatitis,[8] and unripe peaches.[9] An extensive list of compounds causing hemolysis in G6PD deficiency is readily available in standard textbooks of hematology, but the frequency of appreciable hemolysis associated with each of the listed agents is not. In this patient, the history of fava bean ingestion was emphatically denied by both parents, as was a large number of possible agents known to induce hemolysis in G6PD deficiency. Only when the vernacular term for fava bean (yewdow) was used was a history of fava bean ingestion obtained. Yewdow is a popular snack food in Asia similar to potato chips or peanuts in America. Within the Cantonese community, it is known as *chundow.* A photograph of the beans may be helpful when attempting to elicit an accurate history (Figure 1). As the cultural and ethnic diversity increases in the western United States, added knowledge of these differences is required to properly inform patients of pertinent inciting agents to avoid within their cultural milieu.

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Neurogenic Diabetes Insipidus in an Initially Healthy Neonate

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NEUROGENIC DIABETES INSIPIDUS in the newborn period is rare but has been described previously in neonates with infections, congenital brain malformations, intraventricular hemorrhage, and hypoxia.[1-4] This report concerns a 21-day-old infant with central diabetes insipidus in whom no predisposing factors were evident at the time of diagnosis.

Report of a Case

The patient, a 21-day-old female infant, was born to a 20-year-old primigravid woman at 38 weeks' gestation after an uneventful pregnancy. The vaginal delivery was without complication. The infant weighed 3,200 grams (7 lb 1 oz) at birth. She had mild transient tachypnea of the newborn that did not require supplemental oxygen and resolved spontaneously within 12 hours. The baby nursed well while in the hospital and was discharged home on the third postpartum day, weighing 3,062 grams (6 lb 12 oz). Office visits at 10 days and 20 days of age dealt with parental concerns of feeding difficulties and hard stools. Because of progressive vomiting, diarrhea, lethargy, and irritability, however, the infant was admitted to hospital at 21 days of age for evaluation. The parents had not noted the baby to have fever. Of significance was that they had been feeding the patient strained water boiled with rice and caraway seeds, which the infant preferred over formula or breast-feeding.

On physical examination, the infant was lethargic. Her temperature and vital signs were normal, and she weighed 3,200 grams (7 lbs 1 oz). The general physical findings were within normal limits, with the exception of dry mucous membranes and decreased skin turgor, indicating an approximately 5% dehydration. The initial laboratory studies elicited the following values: serum sodium 157 mmol per liter, potassium 4.9 mmol per liter, chloride 127 mmol per liter, carbon dioxide 16 mmol per liter, blood urea nitrogen 8 mmol per liter (normal, 3.0 to 6.5), and creatinine 71 μmol per liter (0.8 mg per dl [normal, 50 to 110 μmol per liter]). A leukocyte count was 11.6×10^9 per liter with polymorphonuclear neutrophils 0.22 and lymphocytes 0.72. The hematocrit was 0.48. The initial urinalysis revealed a specific gravity of 1.003, and the results were otherwise normal. A sepsis workup consisting of urine, cerebrospinal fluid, and blood cultures was negative for pathogens.

The infant was hydrated with an intravenous solution of 5% dextrose-isotonic fluid at 150 ml per kg per day after an intravenous bolus of 10 mg per kg of body weight. By 18 hours after admission, the infant's hydration status was slightly improved. Her weight had increased only 50 grams to 3,250 grams, and the urine output remained elevated at 4.3 ml per kg per hour. The child remained somewhat lethargic, and the electrolytes were only modestly corrected, with a serum sodium level of 151 mmol per liter, potassium 4.1 mmol per liter, chloride 129 mmol per liter, and CO_2 22 mmol per liter. Serum and urine osmolalities were 480 and 50 mmol per kg, respectively. Despite intravenous rehydration, her weight 24 hours later had increased only 35 grams and her urine output remained high at 5.6 ml per kg per hour. Diabetes insipidus was suspected, and a diagnostic argipressin (8-α-arginine vasopressin) infusion was administered intravenously at a rate of 0.3 units per kg per hour over a period of ten hours. Twelve hours after the infusion was started, the serum and urine osmolalities were 288 and 485 mmol per kg, respectively, and the urine specific gravity had risen from 1.003 to 1.022. The infant's weight increased 75 grams to 3,335 grams, and the urine output decreased to 3 ml per kg per hour. Treatment with desmopressin acetate, 0.05 ml given intranasally each morning, was begun, resulting in a return to normal of her serum electrolytes and urine specific gravity. The following day her weight had increased another 85 grams to 3,420 grams. Because of an increased nighttime urine output, however, and a nocturnal decrease of the urine specific gravity, the dosage of desmopressin was changed to 0.025 ml twice a day. Further evaluation for the source of the diabetes insipidus was undertaken and revealed the following normal results: a random serum cortisol level

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TABLE 1.—*Causes of Neurogenic Diabetes Insipidus in the Neonatal Period*

Intracranial defects
Holoprosencephaly
Septo-optic dysplasia
Infections
Listerial sepsis
Meningitis—streptococcal
Meningococcal septicemia
Intracranial tumors
Trauma
Intraventricular hemorrhage
Brain death

of 121 nmol per liter (4.4 μg per dl [normal, 110 to 520 nmol per liter]), thyroid-stimulating hormone level of 3.9 mU per liter, an unenhanced brain computed tomographic scan showing no intracranial defects, normal optic nerves and septum pellucidum, and normal plain films of the skull and long bones.

The infant had complete resolution of vomiting and lethargy, and the findings of a physical examination on discharge were completely within normal limits. She was feeding well on formula and was sent home on a regimen of intranasal desmopressin. At 12 weeks of age she was noted to have poor response to visual stimuli. An ophthalmologic examination revealed nystagmus and hypoplastic optic nerves—approximately 10% normal size. The diagnosis of de Morsier's syndrome (septo-optic dysplasia) was made.

Discussion

Neurogenic diabetes insipidus of neonates usually presents in a patient with known predisposing risk factors (Table 1). As such, the neonate is typically being treated or followed for the preexisting conditions, and diabetes insipidus is discovered because of abnormal laboratory values or urine output. The patient we describe presented with diabetes insipidus at 21 days of age with no known predisposing conditions, and an initial workup proved uninformative regarding a cause. Of interest is that the baby reportedly preferred water over formula since birth, although previous physical examinations revealed no signs of dehydration. Additionally, eye movements and gross visual responses were noted to be normal in the newborn nursery. A further evaluation at 3 months of age revealed diminished visual responses and findings consistent with de Morsier's syndrome (septo-optic dysplasia).

The de Morsier's syndrome is caused by congenital midline brain malformations thought to occur at 6 to 8 weeks of gestational age and involves cerebral structures, optic nerves, pituitary gland, and the hypothalamus to a variable degree. It usually affects the offspring of young primigravid mothers (which was the case in this patient). Unlike the patient described here, infants with de Morsier's syndrome usually present with ophthalmologic abnormalities as the chief parental concern.[5] The endocrine abnormalities are found subsequently and can be multiple or isolated, although growth hormone deficiency is the most consistent abnormality. Approximately 40% of patients will have an absence of the septum pellucidum, although its presence or absence does not correlate with endocrine abnormalities.[6] Again, the patient we described had a normal septum pellucidum.

This case exemplifies the need for continued follow-up to determine the cause of central diabetes insipidus in an infant once the diagnosis has been made. Greger and co-workers reported that in a series of 58 children, the cause of diabetes insipidus could eventually be found in more than 90% of patients.[7] An ongoing evaluation of patients with diabetes insipidus in whom no obvious cause is evident should include a computed tomographic scan of the brain at intervals, repeated evaluations of the hypothalamic-pituitary axis, and astute physical examinations.

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Occult Retroperitoneal Carcinoid Tumor With Flushing and Solitary Lung Metastasis

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FLUSHING is the hallmark symptom of the carcinoid syndrome, occurring in 63% to 96% of affected patients.[1-4] By the time of overt symptoms, patients with carcinoid syndrome usually have liver metastases and pronounced elevations in urinary 5-hydroxyindoleacetic acid (5-HIAA), and the diagnosis is straightforward. We describe the diagnostic challenge of a patient with flushing who had initially normal to minimally elevated urinary 5-HIAA levels and a small pulmonary nodule and later was shown to have an occult metastatic carcinoid tumor of apparent retroperitoneal origin. His dramatic response to the long-acting somatostatin analogue, compound SMS-201-995 (octreotide [Sandostatin, Sandoz Research Institute, East Hanover, NJ]), with relief of subsequent intractable abdominal pain is also reported.

Report of a Case

The patient, a 58-year-old man, had mild facial flushing and intermittently loose stools in April 1985. That fall, his internist measured 24-hour urinary 5-HIAA concentrations on three occasions, with values of 40, 43, and 60 μmol per day (normal 10 to 52), and abdominal computed tomography

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
5-HIAA = 5-hydroxyindoleacetic acid

(CT) showed mild retrocrural and periaortic adenopathy with no evidence of liver metastasis. His initial chest x-ray film was normal. A urinary histamine level was slightly elevated at 75 μg per 24 hours (normal 17 to 68), but a bone marrow aspiration biopsy specimen did not show mastocytosis. The blood serotonin level (SmithKline Bio-Science Laboratories, Van Nuys, Calif) was 2.51 μmol per liter (normal 0.28 to 1.14), and a plasma calcitonin level was 6 ng per liter (normal <19). Vasoactive intestinal polypeptide and substance P levels (A. I. Vinik, MD, University of Michigan Medical School, Ann Arbor) were undetectable—less than 10 ng per liter and less than 25 ng per liter, respectively. A follow-up abdominal CT scan six months later was unchanged; a chest CT scan with 0.5-cm cuts showed a 6-mm right inferior lung field nodule. Serotonin levels gradually rose, yet urinary 5-HIAA concentrations remained normal. In early 1987, a chest x-ray film showed that the nodule had increased in size to 8 to 9 mm with unchanged findings on an abdominal CT scan. No evidence suggested that the minor abdominal lymphadenopathy (nodes ≤1 cm), which had remained unchanged over a two-year period, represented carcinoid metastases. The patient finally consented to wedge resection of the right middle lobe. A localized carcinoid nodule was removed, but postoperatively his flushing persisted.

Intestinal pseudo-obstruction with abdominal pain occurred three months later, and for the first time small liver metastases were noted by CT and magnetic resonance imaging. Angiography showed extensive mesenteric encasement and splenic artery occlusion consistent with an unresectable infiltrative mass lesion deep at the root of the mesentery in the region of the pancreatic head (not visualized by CT or magnetic resonance imaging). Large venous varicosities draining into the caval system were noted in the retroperitoneal area.

Intractable abdominal pain ensued with nonobstructive nausea, vomiting, and weight loss, and the 24-hour urinary concentration of 5-HIAA increased to 345 μmol. Octreotide therapy was begun in August 1987, and the dosage was gradually increased to 200 μg subcutaneously twice a day. Within two months, his abdominal pain decreased considerably, with a reduction in flushing and diarrhea to once or twice a month. As of November 1988, he had gained 8 kg (18 lb) and was free of flushing and abdominal pain with the discontinuation of narcotic analgesia ten months before. Urinary 5-HIAA concentrations fell to 40 μmol per day. A follow-up CT scan showed no growth of liver metastasis; no additional metastases were noted. The only complications of octreotide therapy were mild steatorrhea—16.8 grams per 24 hours (normal <7.0)—and gallstones noted by sonography after nine months of treatment; both have remained asymptomatic. Interestingly, dysosmia, which was noted by the patient early in his course, diminished markedly during octreotide therapy.

Discussion

The differential diagnosis of flushing is diverse,[5,6] and the clinical evaluation can be challenging. Provocative testing with ethanol, epinephrine, or pentagastrin[2,7-9] can be done to precipitate flushing in doubtful circumstances, but the results are not specific[5] and the test may induce dangerous tachycardia or hypotension. When used in combination with measuring specific markers such as tachykinins, provocative testing may be diagnostic.[9]

If the clinical suspicion warrants, a search for other hormonal markers should be undertaken in a patient with flushing and normal 5-HIAA levels. Blood serotonin is an excellent marker of carcinoid hypersecretion,[6,8,10-12] as shown in this case. Urinary serotonin[10,12,13] and histamine,[2,10] circulating levels of substance P,[9,11,12] chromogranin,[14] neurotensin,[12] and other tachykinins,[9] and platelet serotonin levels[12,13,15] may also have value as carcinoid markers. Selective tumoral production of 5-hydroxytryptophan, particularly by foregut carcinoids, has been reported,[2,16] but levels of urinary 5-HIAA and serotonin are usually abnormal in these patients[13,16] because of a peripheral conversion of 5-hydroxytryptophan to serotonin and 5-HIAA. Less than 1% of carcinoid syndrome patients present with initially normal 5-HIAA levels.[4]

The carcinoid syndrome may occur in the absence of liver metastases if the primary tumor originates from the bronchus[17,18] or ovary[11,19,20]; this is extremely rare in carcinoids of gastrointestinal origin.[21] Although our patient did not display the intense prolonged flushing variant that has been described in some patients with bronchial carcinoids,[22] a thorough evaluation did not reveal evidence of tumor other than the lung nodule before surgical intervention. Carcinoid tumors of the retroperitoneum and pancreas are rarely encountered in large series of carcinoid syndrome patients.[1-4,23] To our knowledge, our patient's presentation with flushing due to an occult retroperitoneal carcinoid is unique.

The long-acting somatostatin analogue octreotide has received recent approval for marketing in the United States for the treatment of the carcinoid syndrome. Several studies have shown excellent response rates to octreotide in such patients, with reductions in flushing, diarrhea, and urinary 5-HIAA levels[4,24,25] and a reversal of the carcinoid crisis.[26] Overt regression of carcinoid tumors with the use of octreotide has been reported but is relatively uncommon.[4,24,25,27]

Our patient manifested a remarkable and sustained decrease in abdominal pain during octreotide therapy. Crampy abdominal pain in the carcinoid syndrome has been attributed to a direct bowel effect of serotonin[28]; more intense pain is usually due to mesenteric retraction or tumor-related fibrosis with or without small bowel obstruction, mesenteric arterial insufficiency, or stretching of the liver capsule by metastatic tumor. Spontaneous necrosis of large liver metastases may present as an acute abdomen. This effect of octreotide therapy in our patient may relate to decreased hormonogenesis or mesenteric tumor shrinkage below the limits of CT detection; alternatively, octreotide may modulate pain as a neurotransmitter in the peripheral or central nervous system.[29] Our results suggest that octreotide therapy should be considered in a patient with carcinoid with notable nonobstructive abdominal pain, even in the absence of troublesome flushing or diarrhea.

Steatorrhea appears to be a dose-related side effect of octreotide therapy[24,30]; it rarely presents a clinical problem other than transiently bulky stools at the time of dosage escalations. Endogenous somatostatin excess is associated with gallstone formation,[31] and gallstones and occasionally overt cholecystitis have been reported in patients treated long term

with octreotide.[4,32,33] We recommend monitoring all patients during long-term octreotide therapy with periodic gallbladder sonography.[33]

A final clinical caveat is our patient's altered olfactory sensation at the onset of carcinoid symptoms with subsequent clear-cut subjective improvement after octreotide therapy. This may represent a new feature of the syndrome related to neurohumoral secretion[34] that has not been reported previously.

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Topics in Primary Care Medicine

The Care of Asymptomatic HIV-Infected Patients

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Series' Editors

An estimated 1 to 1.5 million persons in the United States are infected with the human immunodeficiency virus (HIV). Progression from exposure to the acquired immunodeficiency syndrome (AIDS) is slow, taking six years to develop in about 20% of HIV-infected persons and nine years in an estimated 50%.

Increasingly, HIV-infected patients seek the advice of primary care physicians while they are still asymptomatic. Many patients are well informed about the disease and are interested in treatment protocols. Others seek information about prognosis and infectivity and about social and psychological support. To address these concerns, physicians need to evaluate each patient's clinical status. Because many patients present with subtle signs and symptoms of HIV infection, is the patient truly asymptomatic? Is there evidence of a treatable coinfection? What health maintenance measures should be taken? Is the patient eligible for any treatment protocols? Is the patient using "alternative" or experimental therapies—drugs such as dextran sulfate—obtained from community sources?

Clinical Evaluation

Because the duration of infection may predict the likelihood of progression to AIDS, patients should be asked when they may have been exposed. A history of comorbid infections such as tuberculosis, syphilis, hepatitis, herpes simplex, or herpes zoster should be ascertained. Birthplace and travel history may provide clues to the diagnosis of endemic infections, such as histoplasmosis and coccidioidomycosis.

Because many of the early symptoms associated with HIV infection are subtle, patients may not mention them. Similarly, the early signs of infection may manifest themselves in organs that are often given only a cursory examination in asymptomatic patients. Table 1 presents a directed review of symptoms and signs in HIV-positive patients.

Baseline laboratory studies should usually include a complete blood count with differential cell and platelet counts, sedimentation rate, lactic dehydrogenase level (LDH), and an absolute T-helper cell (CD4) count (Table 2). Common abnormalities associated with HIV infection include anemia, leukopenia (especially lymphopenia), and thrombocytopenia. Although the sedimentation rate is a nonspecific test, some clinicians use it to follow the progression of HIV disease. The sedimentation rate tends to increase gradually with the duration of HIV infection, and an abrupt increase is frequently seen in patients with a new opportunistic infection or malignant lesion. A baseline LDH level is useful for future diagnostic evaluations because abrupt increases in LDH values are consistent with *Pneumocystis carinii* pneumonia or B-cell lymphoma.

CD4 counts are used increasingly to monitor the immunologic status of HIV-infected patients. Food and Drug Administration (FDA) guidelines include CD4 counts as a criterion for the use of zidovudine (AZT) and inhaled pentamidine. While the absolute counts are dependent on laboratory techniques and may vary even for a particular patient—especially with concurrent viral infections—the trend of decreasing counts over time has been associated with a poor prognosis. Opportunistic infections seldom develop in patients with CD4 counts greater than 450 cells per μl. Patients with counts less than 200 cells per μl are at high risk for progression to AIDS. Because the trend in CD4 counts is more helpful than any individual value, it may be advisable to check counts every three to six months in asymptomatic HIV-positive patients.

Patients frequently request additional tests such as the β_2-microglobulin (a major histocompatibility protein that is elevated when cell turnover is high) and p24 antigen (a core protein produced by actively replicating HIV). While these two tests are predictive of the prognosis, they are not widely available and their usefulness is still under investigation.

Although an initial chest x-ray film is unlikely to detect disease missed by physical examination and review of systems, a baseline film is useful for comparison if future x-ray studies show questionable interstitial changes or mediastinal adenopathy.

Comorbid Infections

Physicians should screen for treatable or transmissible diseases such as tuberculosis, syphilis, and hepatitis B. The evaluation for tuberculosis should include a purified protein derivative (PPD) skin test and a control skin test (such as

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
CSF = cerebrospinal fluid
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
LDH = lactic dehydrogenase
PPD = purified protein derivative
RPR = rapid plasma reagin

Candida albicans antigen or cell-mediated immunity panel), and a chest x-ray film. While anergy is related to the duration of HIV infection, more than 30% of patients with AIDS and active *Mycobacterium tuberculosis* have positive PPD skin tests. Clinical and radiographic signs of tuberculosis may be atypical and can include extrapulmonary disease. Because patients may be anergic, those whose chest roentgenograms show an infiltrate in any location—especially when associated with hilar or mediastinal adenopathy—should have sputum smears and cultures for mycobacteria. Patients with acid-fast bacilli on a sputum smear should be treated with a regimen of a minimum of three drugs for *M tuberculosis* until a definitive diagnosis is made. Patients infected with HIV who have a positive PPD—greater than 5 mm of induration—and a normal chest x-ray film should receive isoniazid for 12 months.

TABLE 1.—*Review of Systems and Physical Examination for Patients Infected With the Human Immunodeficiency Virus*

	Symptoms and Signs
Review of systems	
Systemic	Anorexia, weight loss, fevers, night sweats
Skin	Pruritus, rashes, pigmented lesions
Lymphatics	Increased size of lymph nodes
Head, eyes, ears, nose, and throat	Headache, change in vision, sinus congestion
Cardiopulmonary	Cough, dyspnea
Gastrointestinal	Dysphagia, abdominal pain, diarrhea
Musculoskeletal	Myalgias, arthralgias
Neurologic	Memory loss, neuralgias, motor weakness, depression
Physical examination	
Skin	Seborrhea, folliculitis, Kaposi's sarcoma (KS) lesions, psoriasis, tinea, herpetic lesions, molluscum
Eye	Visual acuity and fields, cotton-wool and hemorrhagic fundal exudates
Mouth	Hairy leukoplakia (white plaques along lateral aspect of tongue), thrush, oral ulcers, KS lesions
Lymphatics	Asymmetric, tender, enlarged nodes
Cardiopulmonary	Rales, murmurs (in intravenous drug users)
Gastrointestinal	Hepatosplenomegaly
Rectal	Perianal herpes, condyloma, fissures, proctitis
Neurologic	Focal findings, altered mental state

TABLE 2.—*Recommended Laboratory Studies*

Initial Visit	*Follow-up Visits*
Complete blood, differential cell, and platelet counts	Every 3 months or if change in symptoms or signs
Erythrocyte sedimentation rate, lactic dehydrogenese level	If change in symptoms or signs
CD4 cell count	Every 3 to 6 months
PPD skin test plus controls	Yearly
Rapid plasma reagin or VDRL test, or both	Yearly
Hepatitis B surface antigen and antibody	No follow-up needed
Chest x-ray film	If change in symptoms or signs

PPD=purified protein derivative

Because of the high incidence of syphilis in HIV risk groups, every patient should have a rapid plasma reagin (RPR) or VDRL test. If either or both tests are positive, the patient should have a specific treponemal antibody test such as the fluorescent treponemal antibody absorption or microhemagglutination *Treponema pallidum* test. Because HIV-infected patients have impaired antibody production, even low RPR or VDRL titers suggest either a new or an inadequately treated previous infection. Several cases of treatment failures have been reported, suggesting a more rapid progression to neurosyphilis in HIV-infected patients. Currently the Centers for Disease Control (CDC) recommend that all HIV-infected patients with a positive RPR or VDRL test for longer than a year, or for an unknown duration, receive a lumbar puncture with cerebrospinal fluid (CSF) cell count and a CSF-VDRL test. Patients with a normal cerebrospinal fluid evaluation should be treated for late latent syphilis—penicillin G benzathine, 2.4 million units given intramuscularly weekly for three weeks—and should have follow-up titers. Patients with pleocytosis or a positive CSF-VDRL test should be treated for neurosyphilis—penicillin G potassium, 2 to 4 million units given intravenously every four hours for ten days, or penicillin G procaine suspension, 2.4 million units given intramuscularly daily, with probenecid, 500 mg four times a day for ten days.

Hepatitis B serologic tests differentiate between patients who are immune, long-term carriers or at risk for infection. Because the prevalence of HIV infection in high-risk groups such as gay men and intravenous drug users currently exceeds that of hepatitis B infection, patients in these groups are likely to have exposure to HIV before hepatitis B. Therefore, those who are hepatitis B surface antibody-negative should be immunized with hepatitis B vaccine. Although HIV-infected patients may have a suboptimal response to the vaccine, 60% to 70% will have an antibody response.

Health Care Maintenance

The CDC currently recommends that pneumococcal and influenza vaccines be given to HIV-infected persons. As with the hepatitis B vaccine, the earlier these are given in the course of HIV infection, the more likely a patient is to have an adequate antibody response. Although live vaccines, such as oral poliovirus vaccine, should be avoided, the CDC recommends that HIV-infected children receive the measles, mumps, and rubella vaccine.

Zidovudine is the only antiviral agent that has been shown to influence the course of HIV infection. The FDA has approved its use in patients who have recovered from *P carinii* pneumonia and in symptomatic patients who have CD4 counts of less than 200 cells per μl. New data suggest that this drug may halt progression to AIDS in persons with CD4 counts below 500 cells per μl.

Prophylaxis for *P carinii* pneumonia is widely prescribed. One regimen, inhaled pentamidine, 300 mg once each month, has received FDA approval as an investigational new drug for patients with CD4 counts below 200 cells per μl. It has little toxicity but is costly and not widely available.

Other prophylactic regimens include the combination of sulfamethoxazole and trimethoprim (one double-strength tablet twice a day), dapsone (100 mg once each day), and the combination drug, sulfadoxine and pyrimethamine (Fansidar, one tablet each week). These oral regimens are less expensive but have greater toxicity. Patients should have their glucose 6-phosphate dehydrogenase levels checked before treatment with dapsone or sulfadoxine-pyrimethamine.

Patients who are using alternative therapies may ask their physicians to monitor for side effects. Others may not volunteer that they are using such therapies but will admit to their use if asked in a supportive manner. While it is impossible to keep abreast of all alternative therapies, it is best to encourage patients to bring in whatever information they have obtained, and it is advisable to consult with local resources such as state medical associations, pharmacists, and AIDS specialists.

The frequency with which HIV-positive patients should be followed may be tailored to the needs of each patient and the style of each clinician. Patients should be taught how to monitor for signs and symptoms that could indicate early opportunistic infections.

Counseling is an important ongoing responsibility of primary care physicians. Specific areas that often need to be addressed are safe sex practices to reduce the risk of infecting others, the loss of partners and friends from AIDS, isolation from family and support networks, the loss of independence, and fear of death. Patients with individual or group insurance should be counseled to maintain insurability by paying premiums promptly and to consider the effect of job changes on their insurance status. They should be advised to designate a "durable power of attorney for health care." There are no conclusive data linking life-style issues to the progression of HIV infection. Nonetheless, clinicians may make prudent recommendations to patients, such as to avoid unpasteurized dairy products, raw meats, alcohol, intravenous drugs, and unprotected sexual activities.

While it may at first seem overwhelming to care for HIV-infected persons, physicians can seek help through local medical societies. In California, information regarding community resources, policy issues, experimental protocols, and alternative therapies can be obtained from the California Medical Association ([415] 541-0900). With the rapidly growing number of AIDS patients, subspecialists will not be able to care for all persons infected with HIV. Many patients will turn to primary care physicians, who bring special skills to their care, including familiarity with the treatment of chronic multisystem disease, a knowledge of health care maintenance issues, and an awareness of the psychosocial aspects of illness.

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Health Care Delivery

Assessing the Economic Impact of AIDS in Local Communities

Current and Projected Costs for San Diego County

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The economic cost of the acquired immunodeficiency syndrome (AIDS) in San Diego County, California, is forecast to increase from $103 million in 1986 to between $502 and $743 million in 1991, rising at a minimum average annual rate of 30% after adjusting for inflation. A greater emphasis on outpatient care and the use of new therapies that increase life expectancy by reducing the frequency and severity of morbidity will decrease the future annual cost of treatment but will have a small effect on total economic costs because of substantial foregone earnings by persons with AIDS. Estimating the economic impact of this disease provides valuable information for formulating effective strategies to treat AIDS patients, to provide education for limiting the spread of the human immunodeficiency virus, and to achieve other health objectives.

(Seidman RL, Williams SJ, Mortensen LM: Assessing the economic impact of AIDS in local communities—Current and projected costs for San Diego County. West J Med 1989 Oct; 151:467-471)

The current human immunodeficiency virus (HIV) epidemic presents a tremendous challenge to society and the medical community. Planning for the management of the acquired immunodeficiency syndrome (AIDS) at local levels has assumed a greater importance in view of the rapid growth in number of newly diagnosed cases.[1] In this article we quantify the economic effects of AIDS on a large community that has not been studied extensively and we outline information required by local policymakers to formulate and implement appropriate planning. We suggest that a similar analysis is needed in other communities for which sufficient data exist.

In our study we focus on one aspect of the AIDS epidemic—the economic impact. The analysis is targeted to the San Diego County, California, community, although some national and state data are used. Of course, the economic aspect is only one of many complex factors that must be considered in formulating society's evolving response to this epidemic. Such information, however, does provide guidance to policymakers responsible for establishing local health priorities and deciding the best allocation of resources devoted to this and other diseases.

Rationale and Methods for Calculating Costs of Illness

The primary objective in computing the costs of different illnesses is to allocate society's limited resources to achieve the maximum total benefit. In view of current legal and political constraints on increased funding of health care, committing additional resources for disease prevention or treatment of patients afflicted with a particular illness may require a reduction in resources available to combat other diseases. Calculating and comparing the relative economic costs of different illnesses may provide valuable information to those who must establish priorities in allocating resources for disease treatment and prevention.

Researchers have used a general conceptual framework to calculate the costs of broad categories of illness[2] and specific medical conditions or personal behaviors such as hypertension,[3] cancer,[4] coronary artery disease,[5] motor-vehicle injuries,[5] and smoking.[6,7] This human capital approach views a person as producing a stream of output throughout that person's entire productive lifetime.[8] One aspect, then, of the cost of illness is the foregone productivity resulting from disability or premature mortality related to the illness in question.

Cost estimates for any illness often vary according to the specific methods used, the data available, and assumptions about future health care costs or rates of incidence and prevalence of disease. Estimates of the economic effects of a disease usually measure the value of resources used as a result of illness during a particular year, regardless of when symptoms first appeared. Alternatively, cost estimates may capture the value of resources associated with an illness for all patients diagnosed in a certain year, where the costs of this illness may extend beyond that year. In this article we present estimates of the cost of AIDS in San Diego County for two different years to maintain comparability with previous national estimates.

Three distinct categories make up the total cost of AIDS. *Direct* costs include the personal costs of medical services provided for patients in treating the illness as well as nonpersonal costs associated with research, education, and blood screening to prevent the spread of the disease or to find a

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

cure. *Indirect* costs measure a person's lost output due to illness-related morbidity and mortality. The discounted present value of this foregone output is estimated separately for specific age-sex populations and is based on future life expectancy and expectations of labor-force participation and earnings.[8] *Psychological and social* costs measure the physical or emotional pain, suffering, and anxiety of persons with AIDS and their families. These costs are often ignored in cost-of-illness studies because of the difficulty quantifying them, although they are undoubtedly large for this disease.

Previous Research on the Cost of AIDS

The limited number of published studies on the economic effects of AIDS reflects the shortage of reliable data and the changing knowledge concerning the progression of this disease. Many early analyses were done before providers became adept at managing care to reduce costs.[9-12]

Several more detailed cost studies have been reported recently, varying considerably in scope, methodology, and data. Scitovsky and Rice estimated that medical cost per AIDS patient was roughly $35,600 in 1986, with total direct and indirect costs in the United States forecast to rise from $8.7 billion in 1986 to $66.5 billion in 1991.[13] Their calculations are based on the cost of medical care provided AIDS patients in San Francisco and are not representative of costs in other regions of the country because of the geographic variation in treatment patterns and primary AIDS diagnoses.[14,15] Pascal estimated lifetime medical costs per case at $70,000 to $150,000 between 1986 and 1991.[16] Kizer and co-workers reported the total billed lifetime medical costs of $42,421 in the 1987-1988 fiscal year based on Medi-Cal (California's Medicaid) expenditures.[15] Studies by Hellinger projected lifetime costs of $57,000 to $60,000 per patient and total national medical costs of $2.2 to $2.6 billion in 1988.[17,18]

Current and Future AIDS Prevalence in San Diego County

The total cost of AIDS in any year can be estimated from the number of patients alive during that year and the costs incurred by a typical AIDS patient. Table 1 shows the reported number of AIDS cases in San Diego County between 1981 and 1988, the estimated number of persons with AIDS who were alive in 1986, and the estimates of AIDS prevalence in 1991. As in previous studies, all incidence data have been increased by 10% to correct for underreporting.[13,18,19] The reported AIDS incidence in 1988 has also been adjusted for late reporting by 11.2%, the same percentage of cases diagnosed in 1987 but reported the following year. These data indicate a definite decline in the rate of growth in the number of new AIDS cases in San Diego County, with an estimated 350 persons with AIDS who were alive in 1986.

Because of the uncertainty regarding future incidence and life expectancy, three different estimates of AIDS prevalence in 1991 were calculated. The first estimate of 972 newly diagnosed AIDS cases in 1991 was derived from projections of the US incidence per capita by the Centers for Disease Control (CDC)[19] and population estimates for San Diego County,[20] with an adjustment for the roughly 42% higher incidence of AIDS in San Diego County than in the entire United States in 1988 (assumed to remain constant through 1991).

The other estimates of AIDS prevalence in 1991 were derived by applying CDC survival probabilities to different extrapolations of the San Diego AIDS incidence through 1991. Estimate B assumes that the rate of increase in the AIDS incidence between 1988 and 1991 decreases annually by 39.3%, which equals the mean decline in growth of new cases between 1985 and 1988. Estimate C assumes that the rate of change in percentage points between 1985 and 1988 continues through 1991.

These three estimates of the AIDS incidence for 1989 to 1991 are shown in Figure 1. While the AIDS incidence under estimate B continues to increase through 1991 (although at a constantly declining rate since 1986), estimate C actually yields a decline in new AIDS cases beginning in 1990. Although this may be an optimistic projection, it is included as a "best-case" scenario.

It is estimated that a total of 1,866 persons with AIDS will be alive in 1991 for estimate A if the incidence-prevalence relationship observed in 1988 remains constant. The number of persons alive with AIDS in 1991 for estimates B and C was calculated by assuming a uniform distribution of the AIDS incidence in each year and applying CDC survival probabilities according to the quarter in which the illness was presumed to have been diagnosed. The mean percentage of persons with AIDS estimated to be alive in 1991 for each year of diagnosis is shown in Table 1 and yields prevalence estimates of 1,573 and 1,262 for estimates B and C, respectively.

Medical Costs of Treating AIDS Patients

The recent study by Kizer and associates found a substantial geographic variation in medical costs for Medi-Cal patients with AIDS,[15] although no estimate was provided for San Diego County. Table 2 shows Medi-Cal expenditures for treating AIDS patients in San Diego County in each of three

TABLE 1.—*Estimates of AIDS Incidence and Prevalence in San Diego County**†

	Reported Cases		Estimated Incidence and Prevalence					
			New Cases, No.				PWAs Alive in 1991, No.	
Year of Diagnosis	New Cases, No.	PWAs Alive in 1986, No.	A	B	C	Mean Percentage of PWAs Alive in 1991, %	B	C
1981-1983	31	3	...	...	...	0.0	0	0
1984	50	6	...	...	...	0.0	0	0
1985	135	92	...	...	...	2.3	3	3
1986	249	249	...	...	...	4.7	12	12
1987	383	...	...	...	...	9.4	36	36
1988	501	...	...	...	...	18.8	94	94
1989	...	...	...	594	564	37.5	223	212
1990	...	...	...	662	557	75.0	497	418
1991	...	...	972	708	487	100.0	708	487

Total Number of PWAs Alive		
1986		350
1991	Estimate A	1,866
	Estimate B	1,573
	Estimate C	1,262

AIDS = acquired immunodeficiency syndrome, PWA = person with AIDS

*From the San Diego County Department of Health Services.
†All figures have been increased by 10% to allow for underreporting.

recent years based on a special analysis of Medi-Cal claims data by the California Department of Health Services. The Medi-Cal expenditure per patient per month declined almost 50% in the year ending March 1987, although average expenditures increased roughly 6% the following year.

The percent of billed charges paid by Medi-Cal varied considerably according to the provider and type of service. Table 3 shows that physicians and hospital outpatient clinics received less than 40% of billed charges for services provided to Medi-Cal AIDS patients, but almost 90% of pharmacy charges were reimbursed. Overall, only 52.6% of billed charges for the treatment of AIDS patients in San Diego County were reimbursed by Medi-Cal. Although hospital inpatient services still dominate AIDS expenditures, all California AIDS expenditures on outpatient care increased from just 12.9% through August 1986 to 25.3% in the 1987-1988 fiscal year.[15,21]

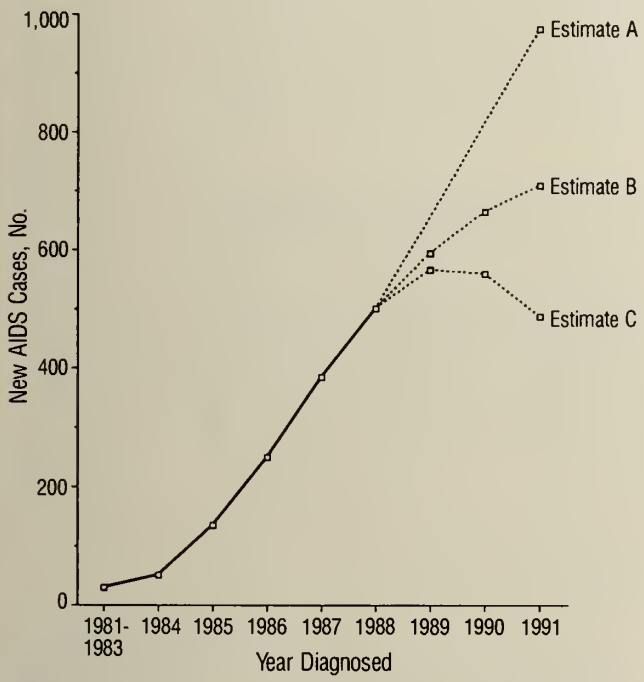

Figure 1.—The graph shows the actual and projected incidences of the acquired immunodeficiency syndrome (AIDS) in San Diego County, 1981 to 1991.

TABLE 2.—*Medi-Cal Expenditures for Treatment of AIDS Patients in San Diego County**

Time Period	*Total Expenditure*	*Total Eligible Months, No.*	*Expenditure Per Person Per Month*
April 1985-March 1986	$ 743,519	204	$3,645
April 1986-March 1987	974,489	497	1,961
April 1987-March 1988	2,041,652	983	2,077

AIDS=acquired immunodeficiency syndrome

*From the California Department of Health Services, Medical Care Statistics Section, Sacramento, Calif.

Expenditures per patient per month for the treatment of AIDS in San Diego County in 1986 were estimated by calculating the weighted mean from per-person-per-month expenditures in 1985-1986 and 1986-1987, where the weights are the proportion of the 1986 calendar year in each time period. The resulting estimate of $2,382 was converted to average annual billed costs of $54,342 by adjusting for the overall percent of billed charges paid by Medi-Cal.

Because most expenditures on AIDS patients are for inpatient care, the billed medical cost in 1991 for persons with AIDS in San Diego County was estimated by calculating the weighted mean charge in 1987 and inflating it by 24.6%, the cumulative projected increase in the hospital input price index (Anne Vanek, Office of the Actuary, Health Care Financing Administration, oral communication, August 1988). The resulting estimate of $58,188 is midway between the low and high estimates by CDC of the medical cost per AIDS patient in 1992.[19]

Nonpersonal direct and indirect costs of AIDS in San Diego County were estimated for 1986 and 1991 from corresponding national cost estimates in Scitovsky and Rice.[13] These estimates assume that nonpersonal costs in any community are proportional to the number of AIDS cases and that age-sex and earnings profiles in San Diego County and elsewhere in the United States are roughly comparable. Surveillance reports on persons diagnosed with AIDS through 1988 revealed similar age distributions of persons with AIDS in San Diego County and in the United States overall.[22,23] Relatively more AIDS patients in San Diego County, however, are male (96.4% versus 90.8%) and white (81.3% versus 57.6%). Because indirect costs of illness are measured by foregone earnings, these differences suggest that our estimates of morbidity and mortality costs in San Diego County based on US estimates will likely be understated.

The Economic Cost of AIDS in San Diego County

Estimates of the direct and indirect costs of AIDS in San Diego County for 1986 and 1991 are shown in Table 4. The total lifetime cost of AIDS for individuals and society will be greater than these annualized estimates because current average life expectancy after the initial diagnosis is about 18 months among AIDS patients in California.[15]

TABLE 3.—*Medi-Cal Payments to Different Vendors for Treatment of AIDS in San Diego County*†*

Vendor	*Total Billed Charges*	*Medi-Cal Payments*	*Reimbursed Charges, %*	*Medi-Cal AIDS Payments, %*	
				Total	*Outpatient*
Hospital inpatient	$2,785,105	$1,470,935	52.8	72.1	...
Hospital outpatient	410,975	157,443	38.3	7.7	27.6
Physician	362,667	141,376	39.0	6.9	24.8
Pharmacy	229,939	204,424	88.9	10.0	35.8
Other	90,758	67,475	74.3	3.3	11.8
Total	$3,879,444	$2,041,653	52.6	100.0	100.0

AIDS=acquired immunodeficiency syndrome

*From the California Department of Health Services, Medical Care Statistics Section, Sacramento, Calif.
†Data are for claims paid April 1987 to March 1988.

TABLE 4.—*Estimated Economic Cost of AIDS in San Diego County, 1986 and 1991*

Cost of AIDS	Cost in $ Millions: 1986 (n=350)	Estimated Prevalence in 1991: Estimate A (n=1,866)	Estimate B (n=1,573)	Estimate C (n=1,262)	Total Cost, %: 1986	1991
Direct Costs						
Total	$ 25.0	$142.1	$119.7	$ 96.0	24.2	19.1
Personal medical	*19.0*	*108.6*	*91.5*	*73.4*	*18.4*	*14.6*
Nonpersonal	*6.0*	*33.5*	*28.2*	*22.6*	*5.8*	*4.5*
Indirect Costs						
Total	78.1	600.4	506.1	406.0	75.8	80.9
Morbidity	*5.1*	*35.8*	*30.2*	*24.2*	*5.0*	*4.8*
Mortality	*73.0*	*564.6*	*475.9*	*381.8*	*70.8*	*76.1*
Total Costs	$103.1	$742.5	$625.8	$502.0	100.0	100.0

AIDS=acquired immunodeficiency syndrome

TABLE 5.—*Variation in Future Medical Costs of Persons With AIDS (PWAs) in San Diego County*

Hypothetic Scenarios: 25% Lower Treatment Cost	25% Longer Life Expectancy (Net Impact on Medical Costs)	Mean Billed Medical Cost per PWA: In 1991	Lifetime	Total Billed Medical Cost in 1991 (in $ Millions): Estimate A	Estimate B	Estimate C
No	No	$58,188	$86,797	$108.6	$91.5	$73.4
Yes	No	43,641	65,098	81.4	68.7	55.1
No	Yes (10% decrease annual cost)	52,369	97,756	97.7	82.4	66.1
Yes	Yes (25% decrease annual cost)	32,731	61,098	61.1	51.5	41.3

AIDS=acquired immunodeficiency syndrome

The total cost of AIDS in San Diego County was $103.1 million in 1986 based on our estimates of prevalence and medical costs. The cost of medical care provided for persons with AIDS was roughly $19 million, or 18.4% of total cost. Not surprisingly, mortality costs account for more than 90% of total indirect costs and more than 75% of the total economic cost of AIDS because of the young age at which most AIDS patients die.

The cost of this disease is predicted to increase dramatically by 1991, ranging from $502 million to $743 million depending on which of the three prevalence estimates most closely approximates the actual number of persons with AIDS alive that year. This suggests that the cost of AIDS will increase from 387% to 620% in five years, with total costs rising an average of 37% to 48% per year compared with predicted annual increases in hospital costs averaging only 5.5%. The declining importance of direct costs reflects the relatively slower growth forecast for nonpersonal expenditures and medical costs of treating AIDS patients compared with market earnings.

While AIDS is a costly disease to treat, it is important to view the estimates we have presented in the context of costs associated with other illnesses. Although data on the local medical costs of other illnesses are not readily available, national comparisons show that the lifetime medical costs of AIDS patients are roughly comparable with costs of myocardial infarction and motor-vehicle injuries for persons in similar incidence populations and are exceeded by the lifetime costs of patients with end-stage renal disease who are on dialysis.[16,24] The predicted faster growth of the AIDS incidence compared with other illnesses is expected to increase the percentage of all personal health expenditures attributed to AIDS from 0.2% in 1985 to 1.4% in 1991, with the corresponding percentage of total indirect costs increasing from 2% to 12% during the same period.[13,24] Of course, the economic impact of AIDS relative to other diseases will probably vary across communities because of different prevalence rates and variations in treatment patterns for any illness.

Even if our projections of future prevalence are accurate, the estimates of future medical costs shown in Table 4 may change for several reasons. More effective case management and a greater emphasis on outpatient care may reduce the cost of treating any medical condition related to AIDS. In addition, new therapies such as aerosolized pentamidine for the preventive treatment of *Pneumocystis carinii* pneumonia, the use of other drugs individually or in combination with zidovudine (AZT), and possibly the earlier administration of existing medications may decrease medical costs by reducing the frequency and severity of morbidity. This decrease may be at least partially offset by the additional costs of these therapies—including laboratory tests and physician services required to monitor and treat the side effects of the new drug regimens—and by more months of morbidity after the initial diagnosis.

Table 5 shows how our estimates of medical costs in 1991 may vary in response to several of these changes. A greater emphasis on less expensive forms of care will decrease the medical cost of treating AIDS patients by the same percentage in any year. New therapies that reduce morbidity and increase life expectancy will also decrease medical costs in 1991 as long as the reduction in the cost of AIDS-related morbidity exceeds the cost of the new therapies and sup-

porting medical services during the months between the initial diagnosis and any mortality that would have occurred in the absence of the new therapies. Even if annual costs decline, the greater number of months in which to incur medication expenses and to experience AIDS-related morbidity may increase medical costs during a patient's lifetime, as in the third scenario. Separate 25% reductions in annual medical costs associated with both changes would decrease medical costs by 44% in 1991, although total direct and indirect costs of AIDS will fall barely 6% because of the importance of foregone earnings. The net effect of different treatment patterns and new AIDS therapies will clearly depend on the resulting change in annual medical costs and the extent to which life expectancy increases.

These possible variations in medical costs have significant implications for financing medical care for AIDS. For example, expenditures on AIDS patients represent a small percentage of the total Medi-Cal expenditures on all health services (0.73% in the 1987-1988 fiscal year[25]). The rapid increase in AIDS expenditures during the last three fiscal years—419% versus 30% for all Medi-Cal health services[25]—coupled with current legal and political constraints in state spending and the projected increase in the incidence of AIDS, suggests that AIDS expenditures may capture a growing portion of future Medi-Cal budgets. These factors may limit the rate at which public expenditures on other health and nonhealth programs increase.

Discussion

The economic effect of AIDS nationally and statewide is substantial and is predicted to increase rapidly in many communities as future AIDS incidence and prevalence grow. Even if the number of new AIDS cases begins to decline—as is projected for Los Angeles and San Francisco beginning in 1991[26]—the number of surviving patients may still rise for several years because of new therapies that increase life expectancy as well as greater physician experience in managing AIDS-related conditions and in discerning which patients will benefit from these therapies.

If reimbursement levels established by third-party payers also continue to increase more slowly than resource costs, a growing number of providers may follow the recent decisions by several teaching hospitals to limit the treatment of new AIDS patients because of fiscal and capacity constraints (C. Clark, "Owen Clinic Stops Taking AIDS Patients," *San Diego Union,* February 22, 1989, p B1).[15] These actions may have an adverse effect on the care AIDS patients receive, especially in communities where public or teaching hospitals and their physicians provide most of these medical services.

The estimates we have presented probably understate the actual cost of AIDS in San Diego County because the psychological costs for AIDS patients and their families are not included. In addition, the human capital approach, which relies on market earnings to measure a person's productive contribution to society, has been shown to undervalue indirect costs for some persons—for example, women and minorities.[8] Furthermore, our estimates in any year exclude the costs of medical care and morbidity for HIV-infected persons in whom the clinical symptoms of AIDS have not yet developed.

Local health policymakers should consider at least four factors in deciding how to allocate limited resources to achieve the greatest improvement in health for a given population:

- The costs of different illnesses experienced in that community,
- The effectiveness of education and other preventive efforts in reducing the future incidence of different diseases,
- The ability to decrease future medical costs through changes in treatment patterns, and
- The political and administrative feasibility of implementing alternative policies.

We have addressed the first factor, providing information on the current and future economic impact of AIDS in San Diego County.

There is clearly a need to collect detailed data on the cost of providing medical services to AIDS patients and how that cost varies according to the specific diagnosis and treatment modality. Such data collecting would allow more accurate estimates of the local economic effects of AIDS and would facilitate comparisons with costs in other communities to formulate strategies for treating persons with AIDS at a lower cost. Nonmonetary benefits such as improved quality of life due to less AIDS-related morbidity must also be considered in evaluating any possible reduction in medical costs.

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Diagnostic Patterns in Hospital Use by an Urban Homeless Population

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Because patterns of disease and health care system usage by the homeless constitute a neglected area of research in the medical literature, we undertook a retrospective analysis of inpatient records on medically indigent adults, controlling for housing status, to add to the growing body of research in the area of homeless health care. Data on all 4,243 indigent patients admitted over 2 fiscal years (1985 and 1986) under the county medical services program of San Diego County, California, revealed 5.3% (226) to be homeless. The commonest major diagnostic category among the homeless discharges was "diseases and disorders of the skin, subcutaneous tissue, and breast," constituting 21.2% as compared with only 8.7% of the discharge diagnoses for housed indigent persons. Within this major diagnostic category, the predominant diagnosis-related group was cellulitis, accounting for 12.8% of diagnoses in the homeless and only 4.0% of discharge diagnoses in other medically indigent persons. A homeless housing status was also correlated with a higher percentage of discharges with the major diagnostic category of "substance use and substance-induced organic mental disorders" but was negatively correlated with that of "diseases and disorders of the circulatory system."

(Morris W, Crystal S: Diagnostic patterns in hospital use by an urban homeless population. West J Med 1989 Oct; 151:472-476)

In recent years interest in the physical health problems of the homeless medically indigent adult population has increased.[1-3] Although this population group is a difficult one to define demographically, it is generally agreed that it numbers at least a quarter of a million people nationwide and suffers disproportionately from a variety of undiagnosed and untreated health problems.[1,2,4,5] The high proportion of mental illness among homeless adults has been well documented.[6,7] Detailed information on the physical health problems of this population encountered on an outpatient basis has only recently begun to be gathered,[8,9] but an analysis of inpatient data is sorely lacking in the medical literature.

Aside from the ethical responsibility to provide health care for those who are ill but cannot afford payment, research into the physical health of the homeless population is important for several reasons. Not only mental health but also physical health problems, especially those that are chronic, may be the economic or social burden (or both) that initially leads to homelessness or prevents a return to a domiciled situation.

Second, the homeless are not a totally isolated group. Indeed, even when sick they are less able to withdraw from contact with others. Consequently, infectious disease problems of the homeless are public health concerns as well. Most dramatic are tuberculosis prevalence rates among the homeless that are 30 times higher than the nationwide prevalence rate, with asymptomatic infections reported as high as 22% to 50%.[10-13]

Third, in these days of efforts toward budgetary restraint, a better understanding of disease patterns and health care needs would lead to more appropriate preventive and cost-efficient curative programs for the homeless.

Fourth, as pointed out by Wright and co-workers, the material deprivation and environmental exposure inherent to the homeless condition provide a dramatic opportunity to study the effects of life-style and environment on health status.[1] A lower socioeconomic status has been shown to substantially increase the length of hospital stay and total charges,[14] but studies addressing differences in health system utilization within low socioeconomic groups are scarce.

In an attempt to clarify disease patterns and the health care needs of homeless adults, we present a retrospective analysis of 4,243 hospital admissions of medically indigent adults in the central region of the city of San Diego, California. Included in this group are 226 records (5.3%) representing those patients who gave no address on admission and thus were labeled as homeless. Psychiatric disorders requiring inpatient treatment are largely funded under the San Diego County Mental Health Program and for this reason are not represented in this analysis.

Patients and Methods

The findings reported here are from a retrospective analysis of all records of patients admitted to hospital under the San Diego County Medical Services program's central region during the fiscal years 1985 and 1986 (n=4,243). These

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TABLE 1.—*The 6 Most Common Major Diagnostic Categories in Both the Homeless and Housed Indigent Population Subgroups, San Diego, California (n=4,243)*

Major Diagnostic Category	Homeless, n=226* No.	%	Major Diagnostic Category	Housed, n=4,017* No.	%
Diseases and disorders of skin, subcutaneous tissue, and breast	48	21.2	Diseases and disorders of the digestive system	510	12.7
Diseases and disorders of digestive system	27	11.9	Diseases and disorders of the circulatory system	443	11.0
Diseases and disorders of nervous system	22	9.7	Diseases and disorders of the musculoskeletal system and connective tissue	437	10.9
Diseases and disorders of respiratory system	20	8.8	Diseases and disorders of the respiratory system	358	8.9
Injuries, poisonings, and toxic drug effects	16	7.1	Diseases and disorders of skin, subcutaneous tissue, and breast	350	8.7
Substance use and substance-induced organic mental disorders	12	5.3	Diseases and disorders of the nervous system	329	8.2

*Not all patients are included in these listings.

data were supplied by Medicus Systems, the county medical services program administrative contractor, from their standard computer documentation on each admission. The designation "homeless" is defined in various ways in different studies. The Centers for Disease Control, for example, refer to the homeless as "those who do not have customary and regular access to a conventional dwelling or residence."[4] For the purposes of this study, a homeless status was assigned to all patients who did not give an address on hospital admission. During the two-year period analyzed, 226 (5.3%) met this criterion for homelessness. Also included in the data on each admission were identification number, sex, birth date, total days in the hospital, diagnosis-related group (DRG), and total charges during the hospital stay.

Because these data represent the clinical inpatient population of the homeless—that is, those with disease of sufficient severity to motivate their going to an emergency department and being admitted—it cannot be definitively concluded that they reflect the health care concerns of the homeless population as a whole. Indeed, only single adults between the ages of 21 and 64 are eligible for county medical services funding. These requirements exclude children, a subgroup of the homeless population that seems to be increasing.[15] Those homeless persons with Medicare or Medi-Cal (California's Medicaid) coverage would also not be included in this indigent population.

There are many bureaucratic barriers to obtaining eligibility for county funding. Applications, appointments, and interviews are all made more difficult, if not impossible, by a lack of shelter, an address, soap, running water, or a washing machine. It may also be assumed that because of a reluctance to being labeled as a transient, false or borrowed addresses often are given on admission, resulting in an underestimation of the percentage of homeless in the overall group.

As a whole, the selection bias would seem to select against recording homeless admissions, but those who are admitted might be expected to have a more advanced stage of disease. Despite difficulties involved in extrapolating patterns of inpatient diagnosis to the overall homeless population, these data reveal usage trends valuable in planning future health care programs for this group, and when compared with the domiciled indigent population, they can reveal major effects that lack of housing can have on health status.

Relative risk calculations and χ^2 analysis with Yates's correction factor were used to determine significant differences between frequencies of different major diagnostic categories and diagnosis-related groups in the homeless and housed subgroups. Two-way analysis of variance was used to test for the effect of housing status on cost and length of stay in several major diagnostic categories, and Student's *t* testing was applied for between-group differences in mean total cost and length of stay.

Results

The housed subgroup had an average age of 38.6 years ($\pm$12.5 [standard error of the mean]) compared with an average age of 38.0 ($\pm$10.2) in the homeless group. Men predominated in the county medical services group as a whole (66%), but the sex ratio was greater in the homeless subgroup, with 87% men and 13% women. No ethnic background data were available in the records analyzed.

As indicated in Figure 1, "diseases and disorders of the skin, subcutaneous tissue, and breast" (DRGs 257 to 284) made up almost a quarter (21.2%) of all hospital discharge diagnoses within the homeless group during the two years studied but accounted for only 8.7% of the housed-indigent discharge diagnoses. The most prevalent major diagnostic category among the housed group was "diseases and disorders of the digestive system" (DRGs 146 to 190), accounting for 12.7% of their total discharges (Table 1). Discharge diagnoses of circulatory (DRGs 103 to 145) and musculoskeletal

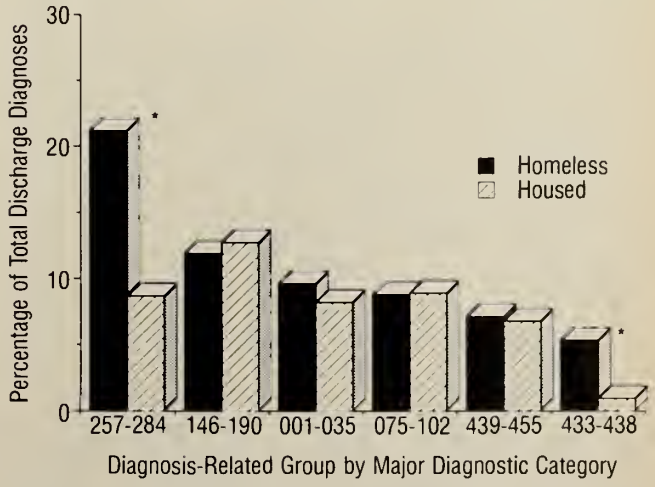

Figure 1.—The graph compares the frequency of the 6 most common discharge major diagnostic categories for 226 homeless indigent adults with the frequency of the same major diagnostic categories in housed indigent adults in San Diego. Diagnosis-related groups 257-284: diseases and disorders of the skin, subcutaneous tissue, and breast; 146-190: digestive system; 001-035: nervous system; 075-102: respiratory system; 439-455: injuries, poisonings, and toxic drug effects; 433-438: substance use and substance-induced organic mental disorders. *$P < .0001$

or connective tissue (DRGs 209 to 256) disorders were second and third most common, respectively, within the housed group but were absent from the top six major diagnostic categories of the homeless. Drug use-related diagnoses were among the six most prevalent categories for the homeless but not for the housed.

Although the average total cost and length of hospital stay were higher in the homeless subgroup (Table 2), these differences were found not to be significant by one-tailed Student's *t* testing. An analysis of each major diagnostic category that was found in at least ten homeless discharge diagnoses revealed large standard deviations, suggesting the presence of outliers that, on a closer analysis of individual DRGs, proved to be present. Two-way analysis of variance showed no influence of housing status on the cost and length of stay ($\alpha=0.05$).

Homeless persons were at an increased risk for both "substance use and substance-induced organic mental disorders" (DRGs 433 to 438, relative risk 5.20, 95% confidence interval 2.94 to 9.22) and "diseases and disorders of the skin, subcutaneous tissue, and breast" (DRGs 257 to 284, relative risk 2.44, 95% confidence interval 1.85 to 3.22) but were at less risk of being discharged with a diagnosis of circulatory disorders (DRGs 103 to 145, relative risk 0.28, 95% confidence interval 0.15 to 0.54).

The combined findings of a high discharge percentage (21.2%) and a relative risk of 2.44 for the diagnostic category of "diseases and disorders of the skin, subcutaneous tissue, and breast" among the homeless subgroup were felt to

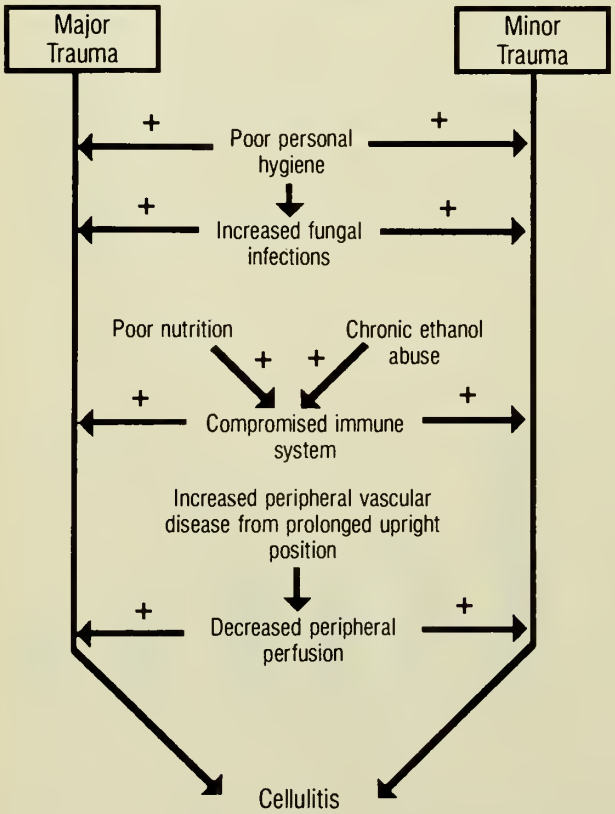

Figure 2.—The schema shows the factors proposed to be influencing the development of cellulitis among the homeless population. The causes of major trauma include accidents and postoperative wounds. The causes of minor trauma include abrasions from sleeping on the ground, insect bites, sunburn and windburn, infected intravenous needle puncture sites from drug use, and poorly fitting shoes.

TABLE 2.—*Mean Total Costs and Total Hospital Days for Homeless and Housed Indigent Subgroups, San Diego, California*

Indigent Subgroup	*Mean Total Cost ×$1,000 (SD), $*	*Mean Total Days (SD), d*	*Cases, No.*
Homeless	7,290.3 (21,542)	7.1 (11.8)	226
Housed	6,778.2 (11,469)	6.2 (7.6)	4,017
Totals	6,805.5 (12,213)	6.2 (7.9)	4,243

SD=standard deviation

warrant a closer analysis. Breaking down this major category into diagnosis-related groups revealed that two of them, "cellulitis, age > 70 years and/or comorbidity or complication" (DRG 277) and "cellulitis, age 18 to 69 years without comorbidity or complication" (DRG 278), made up 60% of all the homeless discharges in this major diagnostic category and 12.8% of all homeless discharge diagnoses. In contrast, these two DRGs made up just 4.6% of the discharge diagnoses for the housed subgroup in this diagnostic category and 4% of the total housed discharges (relative risk 3.55, 95% confidence interval 2.24 to 4.64). The other diagnoses in the homeless group in this major diagnostic category were for skin grafts, skin ulcers, and trauma to the skin, subcutaneous tissue, and breast.

An analysis of total charges and length of hospital stay for cellulitis-associated DRGs showed that homeless admissions were on the average less expensive and shorter than for the same two DRGs in the housed subgroup (Table 3). These differences, however, were not statistically significant.

Discussion

The past stereotype of the homeless as being a predominantly male, white, elderly, and undereducated population suffering from alcoholism or psychiatric disease has been challenged by contemporary demographic data. These data suggest a more heterogeneous population with an average age of 30 to 40 years, made up of at least 50% minority group members, anywhere from 10% to 30% women, and with a considerable proportion having had at least a high school education.[6,16] Ethnic and educational background information was unavailable in these data, but age and sex distribution correlates well with that of earlier studies.

The absence of data on inpatient diagnostic patterns among homeless populations prevents a close comparison of the outcome of this study with other data on homeless hospitalization patterns, but contrast with ambulatory disease prevalence data is possible. Wright and colleagues have analyzed 6,415 outpatient health records of New York City homeless persons[1] and found alcohol and drug problems (32.6%), trauma (30.7%), and upper respiratory tract disease (27.8%) as the most prevalent diagnoses. Cellulitis was classified under "limb disorders" in this analysis, which was diagnosed in 18.8% of this ambulatory homeless population. Comparing these results with geographically matched data from the 1979 National Ambulatory Care Survey revealed that the homeless had a greatly increased prevalence of both "substance abuse" and "limb disease." Although hospital admission records indicate a more advanced and serious degree of disease than those disorders that are handled solely on an outpatient basis, it is reasonable to expect that the most common diagnoses in the outpatient population would lead to an increased prevalence of admissions for the same general categories of disease.

TABLE 3.—*Mean Total Costs and Mean Total Days in Hospital per Discharge for Cellulitis Diagnosis-Related Groups (DRGs) in Homeless and Housed Indigent Population Subgroups, San Diego, California*

	ORG 277*		ORG 278*	
Indigent Subgroup	Mean Total Cost ×$1,000 (SD), $	Mean Total Days (SD), d	Mean Total Cost ×$1,000 (SD), $	Mean Total Days (SD), d
Homeless	4.3 (1.4) n=8	5.9 (2.2)	3.5 (1.9) n=21	4.4 (2.0)
Housed	6.1 (6.5) n=40	7.0 (6.4)	4.3 (2.8) n=12	6.1 (4.3)

SD=standard deviation

*DRG 277 refers to cellulitis in a person aged 70 or older and/or with comorbidity or complication; DRG 278 refers to cellulitis in a person aged 18 to 69 years without comorbidity or complication.

The high relative risk for substance abuse-related problems in the San Diego homeless population is not surprising. A high proportion of substance abuse-related health problems in the homeless is related to alcohol consumption.[17] It is estimated that 40% of homeless persons have a serious drinking problem.[9] What is not clear from studies is to what degree alcohol abuse precipitates homelessness or is a mechanism of coping with the stress of the homeless state.[18] It is interesting that only two persons in the homeless subgroup were specifically given the discharge diagnosis of either "alcohol dependence" (DRG 436) or "alcohol use except dependence" (DRG 437). Because alcohol has a broad range of deleterious effects on the body, it is likely that alcoholism is a secondary diagnosis for a significant percentage of the other admissions.

While the homeless inpatients were at a greater risk of being discharged with substance abuse-related diagnoses than were the housed subgroup, the major diagnostic category of "diseases and disorders of the skin, subcutaneous tissue, and breast" made up a much larger percentage of all homeless discharge diagnoses. In contrast to the chronic, difficult-to-treat disease of alcoholism, cellulitis is readily cured with appropriate antibiotic therapy. More important, cellulitis is often preventable by regular personal hygiene and early intervention. A number of factors inherent to the homeless life-style and environment could contribute to the increased prevalence of skin disease among the homeless subgroup. The immune system of homeless persons likely is weakened by poor nutrition, poor circulatory access to infected areas due to decreased perfusion, and concurrent fungal infections, all of which may contribute to the development of skin infections following serious or minor trauma (Figure 2).

Although analyzing the average total cost and length of stay revealed no significant differences between the homeless and housed subgroups, and two-way analysis of variance of the major diagnostic categories showed that housing status did not have an effect on mean cost and length of stay, calculations reveal that cellulitis alone among the homeless population cost the San Diego County Medical Services system about $100,000 over the two years studied and accounted for a total of 250 hospital bed-days during the same period.

A decreased relative risk in the homeless population of being discharged with the diagnosis of circulatory disorders has not been found in the analysis of ambulatory medical records. Of the diagnoses given in the outpatient New York data, 9.6% were for "heart disease," making it the 12th most common diagnosis, and while comparison with the data from the National Ambulatory Care Survey did not result in as high a ratio as with substance abuse or limb disorders, heart disease was still 1.6 times as common in the homeless group. This discrepancy between inpatient and outpatient data can be explained in part by the fact that the increased percentage of cellulitis-related discharges decreases the percent contribution of other discharge diagnoses. The incidence of hypertension may be another factor. There is an increased prevalence of high blood pressure among the homeless,[19] yet this disease is largely treated on an outpatient basis, effectively removing it as a primary diagnosis in the inpatient population. It is also notable that cardiovascular disease is often an invisible disease. Compared with the dramatic visual nature of skin disorders, the symptoms of heart disorders are much more easily attributed by the homeless to their lack of sleep and poor eating habits that accompany life on the street.

Summary

These data reveal that there are substantial differences in the discharge diagnoses between homeless and housed population subgroups in the city of San Diego. The average cost and length of stay for each subgroup and in each major diagnostic category, however, were not significantly different. Although homelessness conferred the highest relative risk of being discharged with a diagnosis of substance abuse problems, diseases and disorders of the skin made up the largest percentage of homeless discharges overall. It was found that most of the diagnoses within the major diagnostic category of "diseases and disorders of the skin, subcutaneous tissue, and breast" (DRGs 257 to 284) were associated with cellulitis. Unlike findings from ambulatory data sets, it was found that the homeless were at less risk of being discharged with the major diagnostic category of "diseases and disorders of the circulatory system" (DRGs 103 to 145). This decreased risk was attributed to the effect of the increased percentage of persons diagnosed with cellulitis as well as the outpatient treatment of hypertension and the indistinct symptoms of circulatory disorders.

Improved access to the basic elements necessary for personal hygiene, such as soap and water, would be an important first step in decreasing the high percentage of admissions for cellulitis among the homeless. Further measures, such as downtown first-aid stations where nurses and other health workers could provide wound care and a recognition of cellulitis in its early stages, may be indicated as well. Indeed, select members of the homeless population may be capable of self-monitoring skin infections and, if provided with adequate training and simple first-aid kits, act as volunteer community health care workers and educators themselves.

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—ROBERT L. STAMPER, MD

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Commentary

Is Academic Medicine Providing the Best Patient Care?
Some Personal Observations

FRANCESCO GALLATIN BEUF, MD, *Sheridan, Wyoming*

In January 1988, I was admitted to a major teaching and research center because of increasing respiratory distress. The admission eventually extended for two months, with discharge diagnoses of asthma, *Legionella pneumophila* pneumonia, oral herpes, oral and esophageal candidiasis, steroid-induced hyperglycemia, and *Hemophilus influenzae* pneumonia. Other diagnoses that were considered during the admission included Wegener's granulomatosis, pulmonary infarct, allergic bronchopulmonary candidiasis, and aplastic anemia. A number of invasive procedures were required, including bronchoscopy, bronchial biopsy and lavage, bone marrow biopsy, and open-lung biopsy. In other words, I presented a complicated case. Technically my care was excellent.

I am the product of training in major university centers—MD degree from Temple University, Philadelphia (1976); three-year residency in pediatrics at Children's Hospital of Philadelphia (1976 to 1979). Since completing my training, I have served as attending physician in both university-affiliated training centers and in community hospitals. My assumption had been that academic centers provided the best, not only of patient care—at least in complex cases—but also of research and of student, residency, and fellowship training. After my observations during this admission and further reflecting on some of my training experiences, however, I must seriously question certain facets of this basic assumption.

My questions fall into the following categories:

- Does the system of placing staff physicians on clinical services for relatively brief periods of time provide adequate—if not necessarily the best—care to patients and the best clinical experience for physicians?
- Does the academic system tend to foster a concentration on the technical aspects of patients' problems at the all-too-frequent cost of a glaring neglect of such basics as patient nutrition, comfort, and morale?
- Are we generally ignoring the economic consequences of our care plans and are our academic institutions teaching the next generation of physicians, *by example,* that economic considerations are unimportant in patient care?

Clearly I cannot extrapolate my single experience as a patient, attending physician, resident, and student to cover all academic institutions, but some of my observations do have a general application. I will discuss these and make some suggestions for dealing with the problems I have noted.

The first question, that dealing with the assignment of staff physicians, in rotation, to clinical duties, has several dimensions.

A primary consideration is whether the majority of physicians assigned to clinical rotations are willing or able to provide high-quality, hands-on patient care. Good care involves technical skill, the ability to communicate with patients and their families, and the formation of a bond, or pact of trust, between physician and patient. Most academic physicians possess more than adequate technical skills. But those of us who attend medical meetings or read much in the current medical literature are painfully aware of the limitations of medical communication among peers. These limitations are frequently magnified many-fold when an academician is required to explain a complex medical problem to a patient, who is usually a layperson. Assuming that the physician is skillful and is able to communicate with the patient, one of the patient's primary concerns is "Will you stay with me and help me overcome this terrible disease?" When the answer is "Yes, I'll be with you until next Thursday, when my colleague, Dr Wonderful, will take over this service, so I can return to my studies of chemotactic factors," the patient may find it hard to establish a bond of trust in the face of certain abandonment. Dr Wonderful may well live up to his or her name, but a seriously ill patient does not want to take on the added stress of getting to know and trust and learning to communicate with a new physician.

Another consideration, of course, is whether an academic physician really wants to put in a month on the wards while the chemotactic factor research comes to a halt. For some academicians, ward service is a necessary chore, not an exciting privilege. This fact is hard to disguise in their relationships with patients.

My suggestion is that ward service be provided primarily by physicians with demonstrated clinical and communications skills and a strong desire for patient contact. Furthermore, I suggest that ward service extend over longer blocks of time—say, three to four months—or that attending physicians allocate sufficient time to follow through, at least in a consulting capacity, in the care of patients whom they have admitted. For those academic physicians with specific technical skills who either do not wish to serve these blocks of time on the wards or who have a record of difficulty in physician-patient interactions, I suggest that their role be limited as much as practicable to that of consultant and that they not be forced to devote regular segments of time to primary ward service.

All of us, during our training, have been part of those

(Beuf FG: Is academic medicine providing the best patient care?—Some personal observations. West J Med 1989 Oct; 151:477-478)

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flocks of white coats that descend on each patient—particularly the difficult or "interesting" cases—daily to examine chest and oral cavity and quickly review laboratory results. In how many instances have the senior attendings asked the patients how they feel or whether they have any new symptoms, and *listened to the answer?* In how many cases has someone, either the attending or responsible resident, returned and *sat down* to discuss progress with a patient (our body language is disconcerting when we edge toward the door as we ask, "any questions?"), and give that patient time to ask the questions that are really bothering him or her? How many times do we evaluate patients' nutritional status—not just their weight, calorie count, and total protein—but also whether a patient with oral herpes or esophageal candidiasis, for instance, is able to eat the meals being served? How many times do we discuss with both patients and their primary care nurses whether sufficient postoperative analgesia is being given?

Physicians are primarily responsible for patients' care. This is a responsibility shared with the nursing staff, but ultimately it is theirs. If these areas are neglected, assuming that a patient's morale will take care of itself, that the patient's nutrition will be overseen by a dietitian, and that a nurse will attend to the patient's comfort, that assumption may be correct. On the other hand, physicians may provide the best technical care in the world, yet see a patient giving at best a poor response to this care; physicians have all seen how fear, poor nutrition, and discomfort can cause a seriously ill patient to respond poorly or not at all to the best of technical therapy. If physicians neglect to remain personally involved in these aspects of care, patients may feel depersonalized and "used" as a mere teaching tool or intellectual exercise. In these circumstances, the vital partnership between physician and patient is impossible to establish.

Those who have served as attending physicians in academic institutions have a dual responsibility to see that these aspects of care are provided. First, of course, this is the standard of care owed to patients. Second, however, the necessity of this aspect of medicine must be drilled into students and house staff, by example and by demanding that they participate in it themselves.

Some academic centers have responded well to the increasing pressure to control the cost of medical care and are emphasizing cost factors as part of their quality assurance programs and in the academic curricula of their students and house staff. Many, however, still treat cost as a consideration that is somehow unprofessional and inherently detrimental to a patient's care.

In the center where I was admitted, the neglect of cost factors appeared to be the common approach. I experienced a number of flagrant examples of this during my admission and can remember no time when cost was even mentioned in a discussion of choice of care plans among attendings and house staff and students.

Those who teach and practice in these institutions do the profession no favors by treating cost considerations as an insignificant or detrimental aspect of the service. Physicians *must* practice and teach it with skill and enthusiasm or learn to accept its application by bureaucratic fiat. The computer-literate generation of young attendings, house staff, and students should be encouraged to take a strong lead in this endeavor, perhaps by developing cost-estimation programs to be used in the ubiquitous hospital computers. This could not only help to keep costs under medical and not bureaucratic control but also be an area where junior staff and students might set a good example for their seniors.

The above remarks have been directed primarily at academic medicine. This is because the major teaching and research centers are setting the standards that the next generation of physicians is being taught. Many of my observations and suggestions, however, have equal applicability to medicine as it is practiced in the thousands of American community hospitals.

My comments may appear simplistic to some readers. I can assure the general reader, however, that after my experiences as student, resident, attending, *and* patient, I am certain that these are general problems that will require continuing work on the part of all of us.

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GENERAL SURGEON. Established young, mellow but compulsive General Surgeon in southern California seeks an associate so he can spend more time with his young children. If interested send CV and personal description to Number 159, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

CALIFORNIA, ARIZONA OR UTAH YOUR CHOICE

There are private practice opportunities now available in the following Humana California, Arizona and Utah communities:

ORANGE COUNTY, CA

FAMILY PHYSICIANS— Several established, solo FP's with expanding practices in Orange County are now seeking associates. Also, opportunity in extended hours/private practice clinic with six-figure earning potential first year and buy-in option thereafter.

PHOENIX

FAMILY PHYSICIANS—Option to join a group of two, a solo FP who seeks an associate, or purchase two well-established practices.

LAYTON, UTAH

FAMILY PHYSICIANS—Associate needed to join young, board-certified Family Physician in newly opened office. Layton is 12 miles south of Ogden and 15 miles north of Salt Lake City.

NEUROSURGEON—A Neurosurgeon is needed to establish practice. Immediate referrals and generous financial assistance.

For further information, send your CV to: Manager, Professional Relations, Humana Inc., Dept. HH-10, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

(Continued on Page 482)

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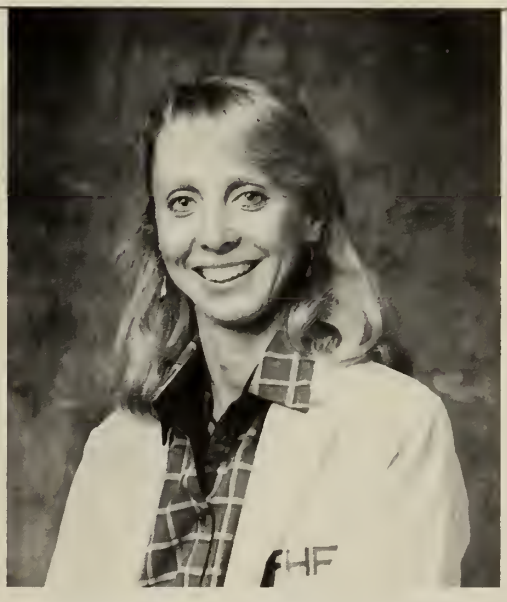

Eva Gentile, MD, joined FHP after completing her residency in Family Practice at Pontiac General Hospital in Pontiac, Michigan. She is currently a member of the American Academy of Family Practice.

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9900 Talbert Avenue, Fountain Valley, CA 92708

Please send more information on medical practice opportunities at FHP.

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- ☐ Arizona
- ☐ New Mexico
- ☐ Utah
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(Continued from Page 480)

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, General Surgery, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful ambulatory health care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE primary care specialists preferred. Contact Bob Morris, MD, FACEP, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

BC/BE INTERNIST being recruited for the community of Artesia, New Mexico. Solo practice with cross-coverage available from local Internist. Community-based financial assistance may be available for the right individual. Family oriented community with year round recreation; excellent weather. Fully equipped 38-bed hospital. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

(Continued on Page 483)

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

MARTINEZ

Emergency Physicians — Join friendly, relaxed and highly professional colleagues at our 204-bed hospital in the heart of the San Francisco Bay Area. We are seeking experienced physicians, BE/BC preferred. Locum Tenens and part-time work available Summer/Fall, 1989 & Winter/Spring, 1990. Recent adjustments provide excellent hourly rate plus paid malpractice. Career positions also available, providing salary and excellent benefits package. Send CV to: Ted Bayer, M.D., Chief, or Andrea Wagner, M.D., Asst. Chief, Department of Emergency Services, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1000, ext. 3316 or (415) 372-1124.

Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

FAIRFIELD

Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including scheduled time off, malpractice insurance, medical, dental and life insurance, and a substantial retirement program. Our physicians are free to concentrate on providing quality health care, without the burdens of managing a practice.

To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

KAISER PERMANENTE

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(Continued from Page 482)

PHYSICIANS WANTED

PROGRESSIVE MULTISPECIALTY GROUP

of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

DERMATOLOGY
OTOLARYNGOLOGY
OB/GYN
NEUROLOGY
ORTHOPEDICS
PEDIATRICS
PODIATRY

Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package, leading to partnership after 18 months.

Reply with CV and references to:

Physician Recruitment
Eaton Medical Group
445 W. Eaton Ave
Tracy, CA 95376

UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is in the second phase of an ambitious development plan and is searching for physicians residency trained in Emergency Medicine. The Health Sciences campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level I trauma center, has paramedic base station training responsibilities, and has a helicopter service. Emergency Physicians supervise medical students, interns, and residents in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

INTERNIST. BC/BE Internist wanted to join Internal Medicine group practice. Competitive salary and excellent fringe benefits. Early partnership. Send CV to Number 162, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602, or call Sara Brenner, (213) 478-5913.

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

PHYSICIANS WANTED

NEUROLOGIST

BC/BE, full- or part-time, for expanding San Francisco bay area private practice with emphasis on clinical Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
240 Polk St
Box 337
San Francisco, CA 94109

GENERAL INTERNIST. Group practice located in beautiful northern California wine country seeks General Internist. We are opening a new 106-bed hospital February 1990; a superb opportunity to join a growing, thriving practice. Excellent salary, benefits, security, and ample time off. Please send CVs to Richard Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

GENERAL PRACTICE—SOUTHEAST WASHINGTON. 32 physician multispecialty clinic needs full-time physician as second physician in Immediate Care Center. Center is part of main clinic and has full range of ancillary and consultative services available. Abundant free time with no on-call responsibility. Excellent school system. Outstanding recreational and cultural opportunities. Guaranteed salary with excellent fringe benefits. Contact Robert Caudill, MD, or David Maloney, Administrator, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720.

SAN FRANCISCO. Well established General Internist seeks BE/BC associate, private practice, some Geriatric emphasis, benefit package includes incentive options, pension funds, malpractice. Contact Martin Lorber, 1500 Southgate Ave, Daly City, CA 94015; (415) 992-4466.

PHYSICIANS WANTED

SACRAMENTO AMBULATORY/URGENT CARE. Part-time openings for Family Practitioners and Internists with experience in adult ambulatory care. Clinic operates 12 hours per day, seven days a week for acute care. Flexible scheduling. Benefits available for physicians working at least six half days per week on a regular basis. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Michael Getzell, MD, Chief, Dept of Internal Medicine, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545.

SAN FRANCISCO. Seeking BE/BC Internist for part-time or full-time locum tenens in busy department of medicine with full subspecialty backup. Excellent salary and full benefits if working six or more half days. California license essential. Contact Paul Feigenbaum, MD, Chief of Service, Kaiser Permanente, 2200 O'Farrell St, San Francisco, CA 94115; (415) 929-2665. EOE.

BC/BE INTERNIST being sought to establish practice in resort community of Ruidoso, New Mexico. Beautiful mountain setting with easy access to all forms of recreation. Financial assistance may be available for the right individual. For more details, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIANS
Immediate Opportunities!
SAN DIEGO

JSA, Inc., is currently offering physicians full, part-time, and PRN positions in a Primary Care Clinic located in San Diego, a JCAHO accredited facility.

BENEFITS PACKAGE

- **Flexible day-time hours**
- **No "on-call" requirement**
- **Paid malpractice insurance**
- **Professional development funding**
- **Incentive programs**
- **Exceptional salary level**

QUALIFICATIONS

- **BE or BC in Family Practice, Emergency Room, or Internal Medicine**
- **MD or DO**
- **Current state licensure**
- **ACLS/BCLS**

Please contact Susan Bray, Recruiting Director at (301) 964-2811, or the Clinic Medical Director at (619) 424-3403.

JSA

HEALTHCARE
Consulting - Management - Services

An Equal Opportunity Employer

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PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- **OB/GYN.** Establish private practice with no investment. Guaranteed income. Hospital has newly designed Single Room Maternity Care and new Women's Health Center.
- **FAMILY PRACTICE.** Guaranteed income while you develop your own private practice. Share beautiful office with young, BC Family Practitioner in a flourishing practice (No OB). No investment required.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some Internal Medicine necessary initially. 112-bed full service hospital with excellent ancillary services.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient.

Located in central California near Sequoia National Park, Tulare offers a family oriented environment, abundant and varied recreation, good schools, restaurants, and shopping. Beautiful, affordable homes close to hospital and office. Strong economy. New businesses are contributing to the steady growth of our active community which combines the life-style advantages of a small city with easy access to all California attractions.

Contact:
Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

GYNECOLOGIST needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648; (405) 225-2511.

NAPA, CALIFORNIA. BC Internist. Location in Napa, heart of the wine country. Close to San Francisco. Offering either professional association or solo practice start-up. Includes attractive income guarantee. Send CV and two letters of recommendation (Department Chief if applicable) to Alvin L. Block, MD, 3230 Beard Rd, Napa, CA 94558; (707) 257-1550.

SAN DIEGO. Well established, multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92018; (619) 295-0599.

PHYSICIAN/INTERNIST, FAMILY MEDICINE

Position is available for a BE/BC MD or DO for a full-time or part-time position in a community-oriented primary care practice. Salary ranges from $50,000 to $58,000. Qualified person should respond to **Comprehensive Health Center, PO Box 13839, San Diego, CA 92113.**

PHYSICIANS WANTED

WASHINGTON STATE
ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY	HEMATOLOGY/ONCOLOGY
CARDIOLOGY	OB/GYN
DERMATOLOGY	RHEUMATOLOGY
INTERNAL MEDICINE	GENERAL SURGERY

FAMILY PRACTICE—permanent, part-time, locum tenens

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

FAMILY PRACTITIONERS AND GENERAL INTERNISTS, Sacramento Kaiser Permanente. Must be BC/BE. Family Practitioners join 23 Family Practitioners with excellent consultant support. Internists work in established Department of Medicine, experience continuing growth. Pleasant practice setting where physicians are free to provide the highest quality medicine with full access to diagnostic and therapeutic services. Affiliated with University of California, Davis, providing a substantial part of their residency programs. Excellent financial package includes in-house CME and retirement package, with no billing or practice management headaches. To join our successful, growing medical group, Family Practitioners send CV to Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825. Internists send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

CALIFORNIA. BC/BE OTOLARYNGOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

AMBULATORY CARE. Join our partnership of established Emergency and Ambulatory Care Physicians. Part-time, full-time, and directorship positions available. Malpractice paid, competitive salary, growth opportunity. Prefer BC/BE in appropriate primary care specialties. If you're interested in a secure, rewarding career position, contact Jane Dressler, California Emergency Physicians, 2101 Webster St, Ste 1050, Oakland, CA 94612-3027.

PHYSICIAN OPPORTUNITIES NATIONWIDE

For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Len Nugent and Co, 1556 Halford Ave, Ste 181, Santa Clara, CA 95051; or call (408) 984-8293, FAX # (408) 984-0412.** Never a fee to the physician.

FAMILY PRACTITIONER. BC/BE to join eight member Family Practice department in multispecialty group. No OB. Near Sacramento. Send CV to Caroline Brown, MD, Dept of Family Practice, Woodland Clinic Medical Group, 1207 Fairchild Ct, Woodland, CA 95695.

ACADEMIC GENERAL INTERNIST. The University of Utah School of Medicine, Division of General Medicine is offering full-time positions for BE/BC Internists at the instructor/assistant professor/associate professor levels. Rank and salary commensurate with qualifications. Opportunities include patient care, teaching of medical students and residents, administration, and clinical research. Applications must be postmarked by October 30, 1989; applications submitted after the deadline may be considered if no qualified candidates have applied by that deadline. An Equal Opportunity Employer. Contact John H. Holbrook, MD, Dept of Internal Medicine, University Hospital 4B-120, Salt Lake City, UT 84132.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist or Family Practitioner at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

PUGET SOUND. BC/BE Family Practitioner for new branch office of multispecialty clinic. Full Family Practice opportunity, OB optional. Guaranteed starting salary and benefits. Respond with CV to Memorial Clinic, Attention: Inge Hart, Personnel, 500 N. Lilly Rd, Olympia, WA 98506; (206) 456-1122, ext 249.

CALIFORNIA, WESTERN STATES, AND TEXAS

Opportunities for BE/BC physicians in ENT, Internal Medicine, Family, General Surgery, Nephrology, Neurosurgery, Pediatrics, OB/GYN, Orthopedics, Urgent Care, and others. *Phone/send CV to* **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0672 or FAX (415) 376-0813.**

(Continued on Page 486)

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(800) 352-7271 (California Only)
(800) 421-2368 (Other States)

(Continued from Page 484)

PHYSICIANS WANTED

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

NORTH CENTRAL IDAHO

17 physician multispecialty group recruiting BC/BE partners.

- 2nd Dermatologist
- 2nd Gastroenterologist
- 3rd General Internist
- 6th Pediatrician

Progressive medical community. Outstanding recreational area. Excellent life-style.

Send CV to:

Bob Baker, Administrator
Valley Medical Center and Children's Clinic
2318 Vineyard Ave
Lewiston, ID 83501
(208) 746-1383

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Internal Medicine, OB/GYN, Occupational Medicine, Orthopedics, General Surgery (breast disease focus), Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIANS WANTED

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy	Otolaryngology
Anesthesiology	Psychiatry
Family Practice	Pulmonary
General and Vascular Surgery	Radiology
OB/GYN	Urgent Care
Orthopaedics	Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

PSYCHIATRIST

BC/BE, part-time, possibly developing to full-time. Expanding San Francisco bay area practice emphasizing Occupational Medicine and med-legal evaluation seeks consulting Psychiatrist. Outstanding reputation, facilities and support staff, established referral base. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
240 Polk St
Box 337
San Francisco, CA 94109

CALIFORNIA. BC/BE HEMATOLOGIST/ONCOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

MD TO ASSIST in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

COLORADO, WASHINGTON, NORTHERN CALIFORNIA. Exceptional practice opportunities now available in Family Practice, Pediatrics, Internal Medicine, Psychiatry, and OB. Send CV to D. A. Franklin, MD, and Associates, 4894 Sterling Dr, Boulder, CO 80301.

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* statewide. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676 or (800) 437-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established group practice. Excellent office, lab, x-ray department. Outstanding community hospital. Submit CV, availability date to John D. Lord, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

SOUTHERN CALIFORNIA. Residency trained Family Practitioner needed for 6 physician Family Practice group. Busy, growing practice averaging 300 new patients a month. Fee-for-service; no HMO patients. Ideal metropolitan location; one mile to beach. Excellent salary plus incentive. Potential partnership in one to two years. Third-year residents are encouraged to apply. Send CV to Lee G. Kissel, MD, South Bay Family Medical Group, 510 N. Prospect Ave, Ste 202, Redondo Beach, CA 90277.

TUCSON, ARIZONA. BC/BE, residency trained Family Physician sought to join busy solo Family Physician in private practice. Attractive start-up package available. Send CV to Herb Jalowsky, MD, 1701 W. St Mary's Rd, Tucson, AZ 85745; (602) 622-1414.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural life-styles. Contact Dr Donn Cobb, Health Officer, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

(Continued on Page 488)

AIM HIGH

A PRESCRIPTION FOR PHYSICIANS

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AIR FORCE

(Continued from Page 486)

PHYSICIANS WANTED

SANTA BARBARA COUNTY FAMILY PRACTICE

California BC/BE Family Practice Physicians sought by Santa Barbara County Health Department for ambulatory practice in Santa Barbara County. Progressive, up to date, and well supported clinical system. Highly qualified physicians will have two to four years experience in county and/or community based outpatient clinics. Fluency in Spanish is highly desirable. Competitive salary DOE. For more information please send current CV to **Elliot Schulman, MD, Santa Barbara County Health Care Services, 300 N. San Antonio Rd, Santa Barbara, CA 93110; (805) 681-5460.** AA/EOE.

ONCOLOGIST NEEDED for multispecialty group practice in Seattle; affiliated with University of Washington. Full-time clinical with potential for research. Diverse patient population includes managed care, fee-for-service, retired and active duty military. Attractive salary plus incentive and excellent benefit package. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine/Emergency Room practice. Five Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. $72k per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

FAMILY PRACTITIONER, BC/BE for community health center. Excellent opportunity in the culturally rich Four-Corners area of northwest New Mexico. Near 110-bed hospital, four physicians with mid-levels in integrated system of health and human services. Outstanding benefit package. Recreational paradise in community of 30,000. Contact Sheila Brenner, Farmington Community Health Center, PO Box 3239, Farmington, NM 87499; (505) 327-4796.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

GENERAL SURGEON BC/BE sought to join Vascular Surgeon in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MARICOPA COMMUNITY MEDICINE ASSOCIATES of Phoenix, Arizona, is staffing 60 plus physicians, physician assistants, and nurse practitioners for Maricopa County's ambulatory care clinics at various locations in the Phoenix metropolitan area. General Practice, Family Practice, and Internal Medicine specialist openings. Maricopa Medical Center, Dept of Community Medicine, 4th Floor, 2601 E. Roosevelt, Phoenix, AZ 85008; (602) 267-5288.

PHYSICIANS WANTED

IMMEDIATE OPENINGS IN CALIFORNIA CENTRAL COAST GROUP PRACTICE

Growing multispecialty group practice
in Ventura, California
seeks Board Certified/Eligible:

- Orthopedic Surgeon
- Pediatrician
- Family Practitioners
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We offer competitive compensation and excellent benefits; shareholdership option after 1 year. Located 60 miles north of Los Angeles, our community is one of the most beautiful areas in California, with excellent schools, a strong economy, and a wide range of cultural and recreational activities. Call for more information. Send inquiries and Curriculum Vitae to:

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PEDIATRICIAN BC/BE sought to join four physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OBSTETRICIAN/GYNECOLOGIST BC/BE sought to join three physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WOFFORD HEIGHTS (FAMILY PRACTICE). Fantastic opportunity for the right physician! New 7,000 square foot multispecialty clinic opened in April 1989 has an opening for a fourth provider. Located in the beautiful mountain lakeside resort community of Wofford Heights, California, an hour east of Bakersfield. Included are pharmacy, full lab and x-ray services. Excellent salary and benefit package. No investment by the physician. Malpractice paid in full. This is a rare opportunity to combine a very attractive life-style and an excellent practice opportunity. We are seeking to contract for physicians now. Call George Johnston, (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

ORTHOPEDIC SURGEON BC/BE sought to join two physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

CLASSIFIED ADVERTISING INFORMATION

(415) 541-0900, Ext 376

(Continued on Page 491)

STOP LESIONS FROM SURFACING

An alarming rise in the incidence of genital herpes points to the need for better disease treatment. Fortunately, long-term maintenance therapy with ZOVIRAX® can help keep herpes patients lesion-free. In controlled studies of 4 to 6 months' duration, recurrences were totally prevented in up to 75% of patients. And during two years of clinical use, daily therapy has been shown to be generally well tolerated.[1] One capsule TID...the best way to stop lesions from surfacing.

Reference: 1. Data on file, Burroughs Wellcome Co

ZOVIRAX®
(acyclovir) **capsules**

Keeps herpes patients lesion-free longer

Please see brief summary of prescribing information on next page.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

Burroughs Wellcome Co.,
Research Triangle Park,
North Carolina 27709

ZOVIRAX®
(acyclovir) capsules

Daily therapy helps keep patients lesion-free longer*

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk consideration in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY—Microbiology).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficacy but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). In a non-standard test in rats, fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS—Short-Term Administration: The most frequent adverse reactions reported during clinical trials of treatment with Zovirax Capsules were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with Zovirax Capsules (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤10 ml/min/1.73 m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottles of 100 (NDC-0081-0991-55), and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light and moisture.

U.S. Patent No. 4199574

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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PHYSICIANS WANTED

WASHINGTON STATE

The Wenatchee Valley Clinic, a multispecialty group of 100 physicians, has several practice opportunities in its Moses Lake branch. Currently we are seeking:

- Dermatology
- ENT
- Family Practice
- Internal Medicine
- OB/GYN
- Ophthalmology
- Orthopedics
- Pediatrics

All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to **Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801;** or call **(509) 663-8711, ext 5205.**

CALIFORNIA DESERT. Part-time Medical Director for adult and child Psychiatric outpatient clinics serving indigent patients and the chronically ill in Needles and Blythe, California. These are small desert communities on the Arizona border and can be reached by automobile from Palm Springs, southern Nevada, and northern Arizona. Duties include evaluations, medication monitoring, supervision, and psychotherapy. Must be California medical licensed and BC/BE. Stipend is $500 per day. Send CV to William R. Mead, Mental Health Systems, Inc, 3420 Camino del Rio N., San Diego, CA 92108; (619) 283-0254.

BC/BE NEUROLOGIST to join progressive San Francisco bay area HMO. Busy clinical practice in desirable Marin County. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Dept of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

ENDOCRINOLOGIST NEEDED to join a busy solo Endocrinologist in a growing southern California city. Established referral base, 300-bed acute care hospital. Competitive salary leading to partnership. Reply with CV to Number 169, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PSYCHIATRIST/PHYSICIAN. Innovative team working with seniors, med evaluations, consultations, some supervision. $78,000 to $104,000 plus benefits for full-time. Part-time also available. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

PHYSICIAN WITH EXPERTISE IN INFECTIOUS DISEASE to establish practice in beautiful western Montana. Missoula is a trade and cultural center and home of the University of Montana. Situated in the heart of year 'round mountain recreational opportunities, it is a hub of skiing, fishing, hiking, and a host of other outdoor activities. Just hours from Glacier and Yellowstone parks. Regional medical center to assist in practice development. First year net guarantee, rent, and managed support. Excellent medical community. Send letter and CV to Grant M. Winn, President, Community Medical Center, 2827 Fort Missoula Rd, Missoula, MT 59801.

CHILD/ADOLESCENT PSYCHIATRIST BC/BE needed for state-of-the-art Behavioral Medicine hospital in Ogden, Utah. Enjoy one-in-five call with high caliber and personable colleagues as you take over a very successful and busy practice. The natural beauty of the mountains and lakes in this area is exceptional as well as the educational and recreational opportunities. Contact Paul Clukies, Jackson and Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987.

PHYSICIANS WANTED

GENERAL INTERNIST. Steinbeck country, BC/BE General Internist to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

CARDIOLOGY. Cardiologist BC/BE to join two other Cardiologists in eight physician multispecialty clinic in Seattle. Extensive invasive/non-invasive opportunities. Send CV to PO Box 364, Seahurst, WA 98062.

SAN JUAN ISLANDS, WASHINGTON. Established, well-equipped 8,500 square foot community-owned clinic with complete emergency facilities seeks two BC/BE ACLS certified Family Physicians. Immediate employment, competitive salaries and benefits. Adjacent 85-bed nursing home. Superb scenic and recreational area. Send résumé to Leonard Eliel, MD, Box 370, Friday Harbor, WA 98250. An EO Employer.

GENERAL INTERNIST NEEDED to join 10 doctor private Primary Care group in San Francisco east bay. Reply to Number 168, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FULL-TIME TRAVEL REQUIRED (one year minimum). Health research organization needs physicians for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individuals will be part of a large medical team conducting health examinations in government examination centers traveling to 88 areas of the US through 1993. Physicians must be licensed in one state and specialized in Internal or Family Medicine. Competitive salaries, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline at (800) 937-8281, ext 8248. Westat, Inc, Rockville, Maryland. EOE/M/F/V/H.

NORTHERN CALIFORNIA. Rapidly expanding HMO in the San Francisco bay area is currently seeking three highly motivated BE/BC Family Practice/Emergency Room Physicians for the Urgent Care Center in a career and/or temporary position. Our 228-bed community hospital offers excellent specialty support, flexible hours, and competitive salaries. Career physicians are offered many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV or contact Edward Cheng, MD, Dept of Urgent Care, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119-1197; (408) 972-6110. EOE.

BAY AREA (San Francisco and Contra Costa counties). Bay Area Addiction Research and Treatment, Inc, is seeking a Medical Director to work in its substance abuse treatment program. The program operates four clinics in the San Francisco bay area with the capacity to treat 1,500 patients. Responsibilities include supervision and training of approximately 20 staff including nurse practitioners, physician assistants, and dispensing nurses. Experience in substance abuse treatment, HIV infection, and primary medical care preferred. Full-time position. Excellent salary and benefits commensurate with experience. Send CV or call Ron Kletter, PhD, BAART, 45 Franklin St, Ste 2N, San Francisco, CA 94102; (415) 552-7914.

WASHINGTON, PUGET SOUND. Excellent opportunity for BE/BC General Internist to share new office and call with three established Internists. Puget Sound community in high growth area. Abundant recreation. Two full-service hospitals. Write Everett Internal Medicine, 1330 Rockefeller #210, Everett, WA 98201. Attn: J. Shaw, MD.

PHYSICIANS WANTED

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Good People. Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

ENDOCRINOLOGIST. Outstanding opportunity for a BC/BE Endocrinologist to join busy hospital-based group in Berkeley. Send CV to Randall Ammon, MD, Endocrinology Dept, 3001 Colby St, Berkeley, CA 94705.

INTERNIST BC/BE needed to join busy pulmonary subspecialty practice in rapidly expanding area near Seattle, Washington. Affiliated with 200 plus-bed and expanding hospital. Other subspecialty welcome, but not necessary. Excellent salary with incentive, benefits, office space, and practice support. Send CV and references to Business Manager, Eastside Pulmonary Associates, 1603-116th Ave NE, Ste #112, Bellevue, WA 98004.

UNIVERSITY PHYSICIANS. Student Health Service, University of Wyoming, Laramie, is seeking physicians for full-time employment. Applicants must have a Medical Doctor's degree plus be BC/BE by either AAFP or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the state of Wyoming. Prefer candidate to have at least four years of primary care experience. Physicians to join two full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. Closing date: October 25, 1989, or until positions are filled. Send inquiries and/or CV to Albert H. Roth, MD, Acting Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, Wyoming 82071. EOE/AA.

RESEARCH DIRECTOR. Direct metabolic research involving the research and development of absorption into stomach and duodenum of iron vitamins through chelating agents for commercial development for pregnant women and persons who have iron deficiency anemia. Research, development, and manufacture of bulk organic or inorganic medicinal chemicals and their derivatives and/or processing (grading, grinding, and milling) herbs and bulk botanical; included are manufacturing Agar and similar products of natural origin as well as manufacture and isolation of basic vitamins. Products include uncompounded gland derivatives. Requires MD degree or PhD in Biochemistry and one year in the job or two years experience as a Medical Metabolic Researcher. $3,841 per month, 40 hours per week. Job/interview: Northridge, California. Send this ad and résumé to Job # BLW7112, PO Box 9560, Sacramento, CA 95823-0560 no later than November 6, 1989.

(Continued on Page 494)

Shown left to right are William Morgan, M.D.; William Singer, M.D.; Rebecca Katz, M.D.; Mitchell Frank, M.D.; Frances de Picciotto, M.D.; Matt Young, M.D.

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(Continued from Page 491)

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DIAGNOSTIC RADIOLOGIST to join five member group covering two small hospitals in northern California. Call (916) 877-8092.

GENERAL SURGEON—SAN FRANCISCO BAY AREA. Small group of well-established, BC General Surgeons is now seeking to add another member with two to three years practice experience. Send CV to Manager, Professional Relations, PO Box 1438, Dept HH-10A, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

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PHYSICIANS WANTED

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UTAH—PEDIATRICIAN. An extremely busy and well-established Pediatrician in Layton, Utah, is now seeking an associate. This physician has two offices, one of which is located next to our 110-bed hospital. Layton, located just 20 miles north of Salt Lake City and 15 miles south of Ogden, has a service area of 140,000, 70 percent of whom are under the age of 35 with large families. For further information, send your CV to Manager, Professional Relations, Humana Inc, Dept HH-10A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

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CARDIOLOGIST—NONINVASIVE/INVASIVE to join four member busy cardiology practice in small town, one hour from Los Angeles. Full range of noninvasive cardiology and active Catheter lab. Position available immediately through July 1990. Send CV to Number 175, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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INTERNIST BC/BE. Progressive San Francisco bay area HMO has a full-time Internal Medicine position and a part-time Urgent Care position available. Busy clinical practice with facilities in San Rafael and Petaluma. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Dept of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

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Inn of the Seventh Mt., Bend

General Surgery Conference
March 2-3, 1989
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Continuing Medical Education
Oregon Health Sciences Univ
Portland, OR 97201-3098
(503) 279-8700

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1990, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1990, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1990, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1989, Missoula.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1990, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1990, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1990, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1990, date and location to be announced.

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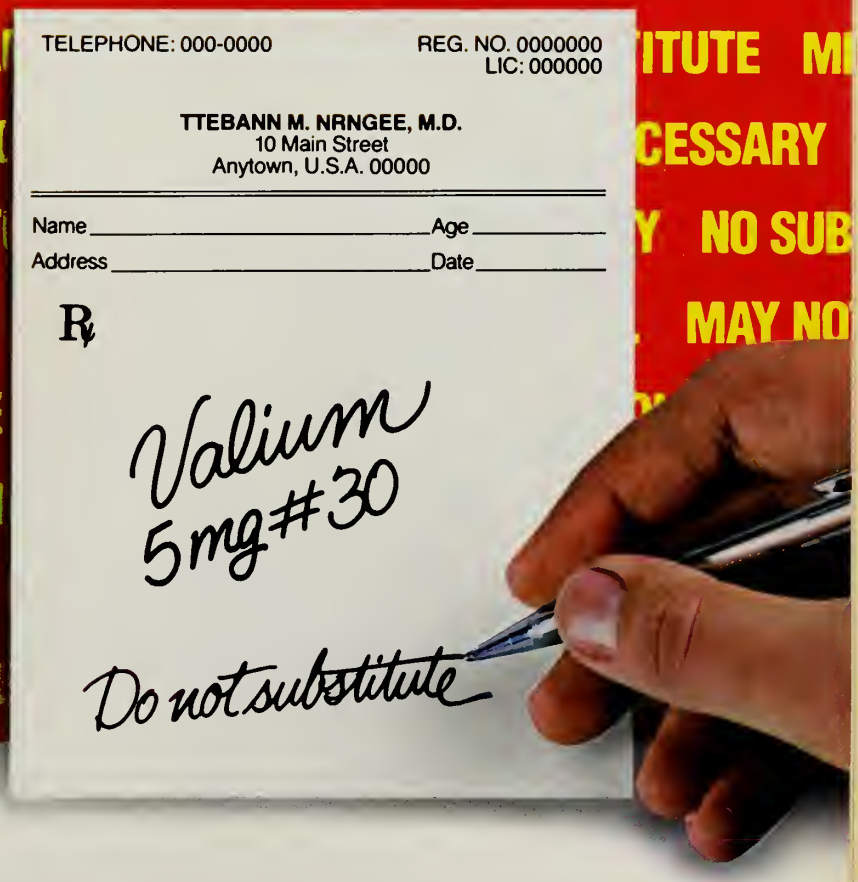

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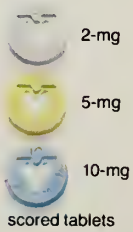

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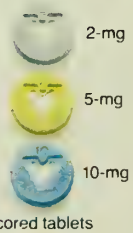

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INDICATIONS AND USAGE. ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **DRUG INTERACTIONS. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL. **Agents Increasing Serum Potassium:** ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Lithium:** Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. **Human Experience:** There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use the ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward

support of blood pressure and renal perfusion with the administration of fluids and pressores as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia. (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response.

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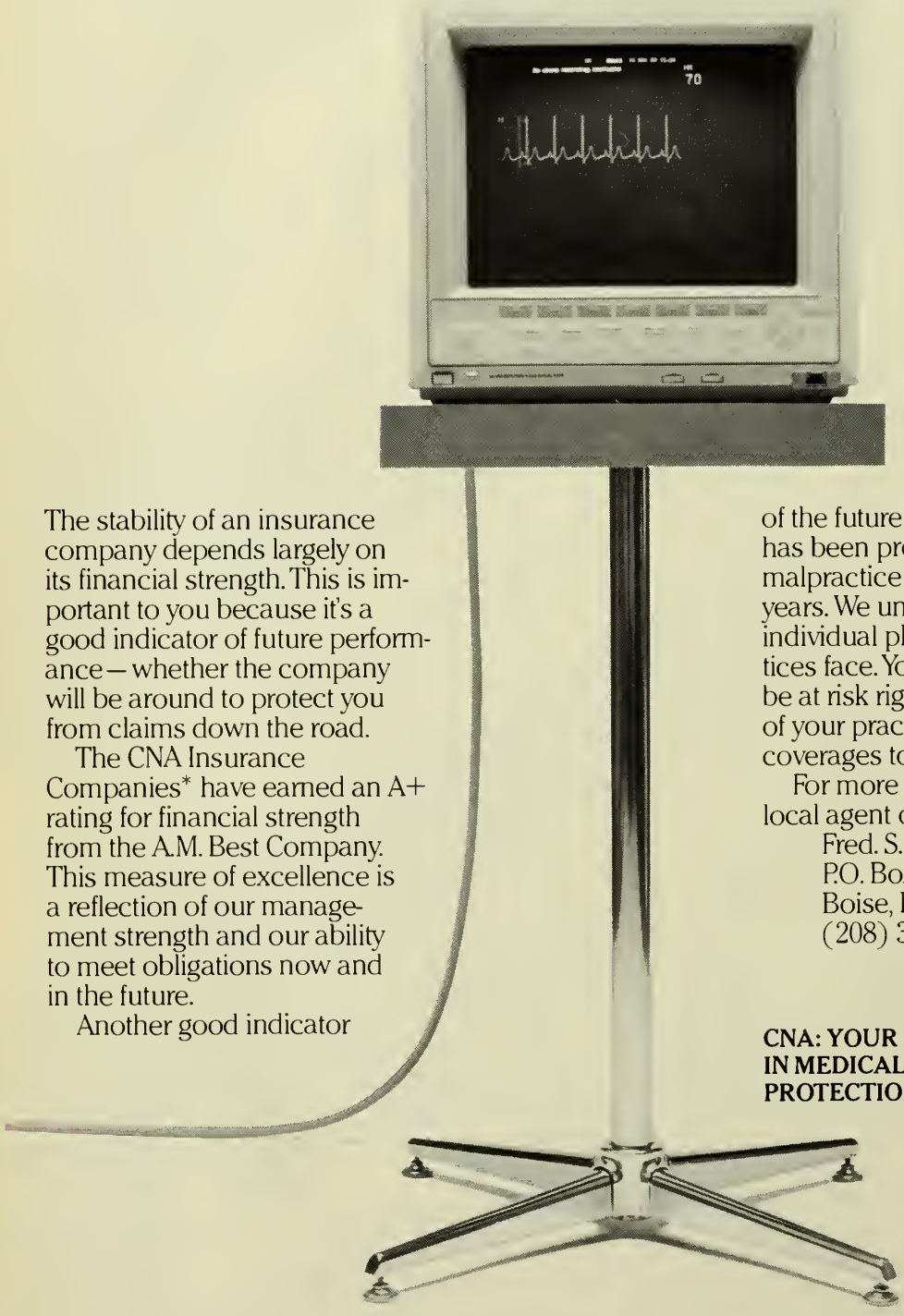

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Manuscripts—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

Clinical Investigation—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

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Placebo-like side effect profile at the 1 mg dose

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The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: General. Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 18—**Techniques in Gynecologic Surgery: Slide and Video Conference.** Ashton B. Taylor Auditorium, Mayo Clinic Scottsdale. Sat. Contact: Jodi Lee Smith, Mayo Clinic Scottsdale, (602) 391-8300.

November 18-19—**Neoplasms and Diseases of the Head and Neck.** Arizona Society of Pathologists, Scottsdale Hilton. Contact: Beverly Reichter, (602) 246-8901.

December 1-2—**External Rhinoplasty Course.** Tucson. Fri-Sat. Contact: Ruth Ann Lynn, (602) 626-7764.

December 2-3—**Arizona Chapter, American College of Surgeons.** Westward Look Resort, Tucson. Sat-Sun. Contact: U of A, CME, (602) 626-7832.

December 13—**Dean's Education Rounds.** Arizona Health Sciences Center, Tucson. Wed. Contact: Jack Roberts, (602) 626-4555.

December 14—**Genetics Update.** Flagstaff Medical Center, Flagstaff. Thurs. Contact: H. Eugene Hoyme, MD, (602) 795-5675 (Tucson) or William Austin, MD, (602) 774-1811 (Flagstaff).

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

January 20—**Current Medical and Surgical Approaches to Urolithiasis.** Mayo Clinic-Scottsdale. Contact: Mayo Clinic-Scottsdale.

February 11-16—**International Congress III: Lasers, Stents, and Interventions in Vascular Disease.** Arizona Heart Institute, Scottsdale. Contact: Erika Scott, (602) 266-2200.

February 16-17—**Geriatrics in a Changing Society: Enhancing Function—2nd Annual Regional, Multidisciplinary Conference.** Samaritan Institute of Gerontology, Phoenix. Contact: Jean Kiernat, (602) 239-5884.

February 23-25—**Anesthesia for the 1990s.** Arizona Society of Anethesiologists, Wyndham Paradise Valley Resort, Scottsdale. Contact: Beverly Reichter, (602) 246-8901.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital. Contact: Barbara Bengtson, (602) 239-4350.

March 1-3—**Rheumatology for the 90s: A Look Into the Future.** Westin La Paloma Resort, Tucson. Contact: CME, Arizona Health Sciences Center, (602) 626-7832.

March 1-4—**A Continuance of Excellence.** Arizona Academy of Family Physicians, The Registry Resort, Scottsdale. Contact: Nancy Reeves, (602) 249-2021.

March 8-10—**Recent Advances in Neurology and Neurosurgery—17th Annual Symposium.** Barrow Neurological Institute at Camelback Inn Resort, Scottsdale. Contact: Toby Jardine, (602) 285-3178.

March 23-24—**Ophthalmic Reviews.** Mayo Clinic-Scottsdale at Scottsdale Sheraton Resort. Contact: Mayo Clinic-Scottsdale.

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ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd. Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 19-21—**Western Society of Allergy and Immunology: 28th Annual Meeting.** Western Society of Allergy and Immunology at Hotel del Coronado, San Diego. Thurs-Sat. $120. Contact: Joyce Gullixon, PO Box 1119, Portland, OR 97207. (503) 224-6159.

ANESTHESIOLOGY

October 22-28—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Stouffer's Resort Hotel, Wailea, Maui, Hawaii. Sun-Sat. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

November 17-19—**UCD Anesthesiology Update.** UCD at Monterey Plaza. Fri-Sun. 12 hrs. $325. Contact: UCD.

January 11-14—**Anesthesia Update 1990.** UCSD at Hotel Del Coronado, Coronado. Thurs-Sun. Contact: UCSD.

January 14-19—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 26-28—**28th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $250. Contact: Katherine Barky, MD, Pediatric Anesthesiology Conference, Children's Hospital, PO Box 54700, Los Angeles 90054.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Sat. Contact: Murray G. Atnikov, MD, PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 9-13—**64th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Fri-Tues. Contact: IARS, 3645 Warrensville Center Rd, Cleveland, OH 44122-5280. (216) 295-1124.

March 24-25—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott Hotel. Sat-Sun. 9 hrs. $125. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

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CARDIOLOGY

October 27-29—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Bally's Casino Hotel, Las Vegas, Nevada. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

November 3-4—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Rancho Las Palmas, Rancho Mirage. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

December 1-2—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 10-12—**Cardiovascular Disease in the Elderly.** UCI at Fess Parker's Red Lion Resort, Santa Barbara. Wed-Fri. Contact: UCI.

January 19-20—**Coronary Heart Disease Update.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $325. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

March 30-31—**Cardiology for the Clinician.** UCI at Long Beach. Fri-Sat. Contact: UCI.

DERMATOLOGY

October 14-15—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF at Laurel Heights Campus. Sat-Sun. 10 hrs. $205. Contact: UCSF.

November 2-5—**International Hot Spots in Dermatology: The Patient, the Disease, the Physician and the Art.** Kauai Academy of Continuing Education at Stouffer's Waiohai Beach Resort, Poipu, Hawaii. Thurs-Sun. Contact: David J. Elpern, MD, PO Box 457, Kalaheo, HI 96741.

January 18-20—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande at Torrey Pines, La Jolla. Thurs-Sat. $400. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 19-21—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess. Fri-Sun. Contact: UCSD.

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

October 19-22—**Traumatic Brain Injury.** UCD at Hyatt Regency, Sacramento. Thurs-Sun. 27 hrs. $415. Contact: UCD.

December 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium II: Trauma and Surgery.** UCSD. Mon-Fri. $450. Contact: UCSD.

December 7-9—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 16 hrs. $220. Contact: UCSF.

December 11-15—**Emergency Medicine Symposium III.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

January 17-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Maui, Hawaii. Wed-Sun. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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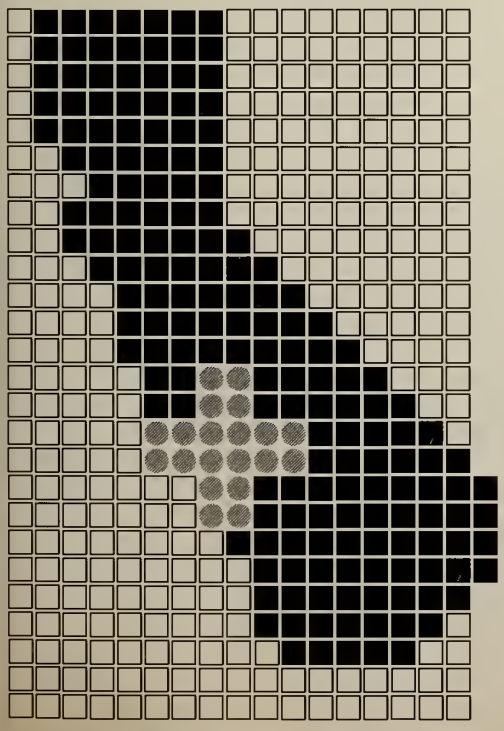

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1. Location of known office of publication: 221 Main Street, 3rd Floor, San Francisco, California 94105.

2. Location of the headquarters or general business office of the publisher: 221 Main Street, 2nd Floor, San Francisco, California 94105.

3. Publisher: California Medical Association, 221 Main Street, 2nd Floor, San Francisco; Editor, Malcolm S. M. Watts, M.D., 221 Main Street, 3rd Floor, San Francisco; Managing Editor, Diana McAninch, 221 Main Street, 3rd Floor, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 221 Main Street, 2nd Floor, San Francisco, California (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.

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7. Average number of copies each issue during preceding 12 months: Total 53,368; paid circulation by mail subscription, 52,655; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier, or other means, 607; total distribution, 53,262; office use, leftover, unaccounted, spoiled after printing, 106; total net press run, 53,368. Single issue nearest to filing date, September 1989: Total 50,477; paid circulation by mail subscription, 49,905; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier, or other means, 445; total distribution, 50,350; office use, leftover, unaccounted, spoiled after printing, 127; total net press run, 50,477. Diana McAninch, Managing Editor.

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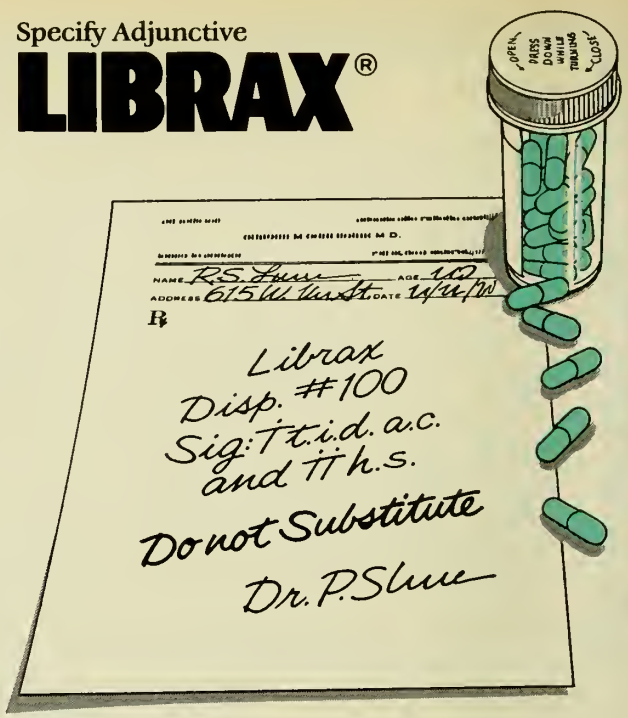

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CONTINUING MEDICAL EDUCATION

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February 17-20—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Las Vegas, Nevada. Sat-Tues. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 18-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Los Angeles. Sun-Wed. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

March 4-9—**11th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences Inc, PO Box 52 B, Newport Beach 92662. (714) 650-4156.

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. Contact: UCSD.

April 7-14—**Cardiopulmonary Emergencies.** American Postgraduate Institute of Postgraduate Education and Scripps Memorial Hospital Encinitas at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. One week. Contact: Edith S. Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

INTERNAL MEDICINE

October 16-18—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Mon-Wed. Contact: Luis M. de la Maza, MD, 101 City Dr South, Orange 92668. (714) 634-6868.

October 21—**Fine Needle Aspiration Tutorial.** UCSF at San Francisco. Sat. $550. Contact: UCSF.

October 21—**Inflammatory Bowel Disease—New Advances.** National Foundation for Iliatis & Colitis at Sheraton Grand Hotel, San Diego. Sat. 7 hrs. $130. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

October 23-27—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 30-November 1—**13th Annual Cancer Symposium.** Scripp Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 18 hrs. $390. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (629) 453-6222.

October 30-November 3—**Hyperbaric Medicine.** Long Beach Memorial Medical Center. Tues-Sat. 36 hrs. $650. Contact: George Hart, Dept of Baromedicine, 750 E 29th St, Signal Hill 90806. (213) 595-3943.

November 2-4—**San Francisco Otology Update: 1989.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 22 hrs. $385. Contact: UCSF.

November 3-5—**Bone and Soft Tissue Tumors Diagnostic Imaging Modalities, Pathology and Treatment.** UCD at Sheraton Sunrise, Sacramento. Fri-Sun. 16 hrs. Contact: UCD.

November 10-11—**Gastro-Intestinal Cancer.** Saint Joseph Medical Center at Century Plaza Hotel, Los Angeles. Fri-Sat. 12 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

December 6—**25th Annual Northern California Cancer Conference.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Morgado, (916) 891-7300, ext 7375.

January 18-21—**Advances in Gastroenterology.** UCSD at Hotel Del Coronado, San Diego. Thurs-Sun. 23 hrs. $425. Contact: UCSD.

January 19-20—**The Medical Dysphagia Team: From Intensive Care to Rehabilitation.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 25-27—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 2-3—**7th Annual Reider Laser-Urology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 3-4—**Searching for New Horizons in Non-Invasive Technology: The Next Decade.** UCSF at Union Square Holiday Inn, San Francisco. Sat-Sun. $200. Contact: UCSF.

February 9-10—**2nd Annual Bristol Myers Symposium on Neurosciences.** UCSD at Price Center, La Jolla. Fri-Sat. 12 hrs. $50. Contact: UCSD.

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 18-25—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. One week. Contact: UCD.

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5-6—**Advanced TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

March 7-8—**Advances in Endocrinology and Metabolism.** UCSF at Stanford Court Hotel, San Francisco. Wed-Thurs. $275. Contact: UCSF.

OB/GYN

November 9-11—**AIDS and Other Sexually Transmitted Diseases.** American College of Obstetricians and Gynecologists at Universal City. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

November 9-12—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. Contact: UCI.

November 12-18—**12th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: UCI.

January 28-February 1—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

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February 2-3—**7th Annual Reider Laser-Gynecology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

March 22-24—**Geriatric Gynecology With Special Emphasis on Urinary Incontinence.** UCI at Palm Springs. Thurs-Sat. Contact: UCI.

April 18-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Wed-Fri. Contact: UCI.

OPHTHALMOLOGY

December 1—**Phacoemulsification and IOL Update.** UCI at Center for Health Education, Long Beach. Fri. Contact: UCI.

December 14-15—**Update: Pediatric Ophthalmology.** UCSF at Hyatt Regency, San Francisco. Thurs-Fri. Contact: UCSF.

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

PEDIATRICS

October 14-21—**14th Annual Pediatrics for the Practitioner.** UCI at Mauna Kea, Hawaii. 1 week. Contact: UCI.

November 3-5—**Current Advances in Pediatrics.** American Academy of Pediatrics California Chapter 4 at Disneyland Emerald Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: California Chapter 4, AAP, PO Box 1297, Orange 92668. (714) 978-2415.

November 4—**Pediatric Protein Metabolism.** UCI at Center for Health Education, Long Beach. Sat. Contact: UCI.

November 13-17—**Postgraduate Institute for Emergency and Primary Care Physicians Symposium III: Pediatrics.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 9-10—**Stabilization and Management of the Critically Ill Child.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. 9 hrs. $150. Contact: UCSF.

January 12-13—**North American Society for Pediatric and Adolescent Gynecology** at Red Lion Hotel, Costa Mesa. Fri-Sat. Contact: UCI.

January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

February 2-4—**Current Concepts in Pediatric Medicine 1990.** Children's Hospital at Hyatt Islandia, San Diego. Fri-Sun. Contact: Children's Hospital and Health Center, Medical Education Dept, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

April 6-7—**Annual Ambulatory Pediatrics.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

PSYCHIATRY

October 26-29—**Psychosomatic Medicine and Consultation-Liaison Psychiatry in a High-Technology World.** Academy of Psychosomatic Medicine at Riviera Hotel, Las Vegas, Nevada. Thurs-Sun. Contact: Academy of Psychosomatic Medicine, 5824 N Magnolia, Chicago, IL 60660. (312) 784-2025.

November 1989-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

November 10-12—**35th Annual Group Therapy Symposium: Focus on Leadership.** UCSF at Sir Francis Drake Hotel, San Francisco. Fri-Sun. 21 hrs. $195. Contact: UCSD.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 25 hrs. $395. Contact: UCD.

February 2-4—**Cognitive Therapy Conference.** University of Pennsylvania Cognitive Therapy and Research Department at Newporter Resort, Newport Beach. Fri-Sun. 16 hrs. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 9-11—**West Coast Psychiatry Board Review.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. 16 hrs. $450. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 24-25—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 12 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

RADIOLOGY

October 28-29—**Advanced Imaging of the Musculoskeletal System.** UCSD at Le Meridien San Diego Hotel at Coronado. Sat-Sun. 12 hrs. $200. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 30-November 3—**14th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $300. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 3-5—**9th Annual Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 10-12 and January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: UCSD.

December 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 20 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 60009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 1-4—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 16 hrs. $375. Contact: UCSD.

March 2-4—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-7—**Neuroradiology Update.** UCSD at Hotel del Coronado, San Diego. Mon-Wed. 18 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-9—**Combined Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Tues-Fri. 23 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**MRI for the Technologist: Symposium and Workshops.** UCSD at Hotel del Cornado, San Diego. Tues-Fri. 21 hrs. $275. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 574)

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Journal of the Arizona Medical Association

ARIZONA MEDICINE

November 1989, VOL. XLVI, No. 11

Physician Entrepreneurism: Is It Our Fault?

Marshall B. Block, M.D.

Physicians have received a lot of heat lately regarding their financial involvement in companies to which they refer patients. This is a departure from the past and is thought by some to represent a major conflict for physicians.

The historical development of such relationships is of interest. The concept of a for-profit operation is not foreign to medicine as it has been there since its inception. Every physician is in a for-profit business. With the increased complexity in the financing of medical care, physician education and business management has by necessity increased. Physicians practice for the most part in increasingly complex and sophisticated arrangements, usually with other physicians in three to five person groups. Gone are the days of the one physician office run by a part-time wife, mother and bookkeeper.

In concert with the Federal Government's implementation of the Prospective Payment System (DRGs), the unbridling of hospital care occurred with a concomitant increase in delivery of out-patient services. The apparent cost effectiveness of this approach led other third party payors in the same direction and the movement "out of hospital" snowballed. Historically, it was physicians who were in the forefront of hospital development in this country. Therefore, it was not unreasonable they would also be the leaders in the development of effective out-patient care. Within our own community, physicians established the first freestanding out-patient center (Surgi-Center) which subsequently was franchised. Similarly, out-patient radiological and laboratory facilities were established by physicians. Physicians felt comfortable in their involvement as they have practiced in similar arrangements previously without obvious difficulty. For instance, every time a physician recommended a course of action in which he had some involvement, whether a chest radiograph in his office or even a return visit, there was the potential for such a conflict.

Thus, part of the explosion in out-patient facilities and physician involvement was the direct result of the Federal Government and the private payor accentuation on out-patient delivery of health care. Now that such facilities exist and are economically viable and apparently cost effective, the Government and other legislative bodies are concerned that a potential for abuse exists. To date, there is no data available to confirm or support such a notion. There is some evidence that physicians who have a vested interest in a facility will order more studies from that facility. However, it is unclear whether this is detrimental to the patient or to the system. It may very well be that greater access and availability may foster more effective medical care.

The key issue which continues to be raised is whether physicians should be placed in such a position. Will the concept of medicine as a "profession" be hurt by such entanglements? Dr. Arnold Relman, editor of the *New England Journal of Medicine*, is the most outspoken proponent of such a position. There is concern that if the business aspects of medicine outweigh our altruism society will view physicians no differently than other providers of services.

Each physician is going to have to weigh this concern when they become involved in such activities. Unfortunately, with the rapid changes in health care delivery within our country, the concept of "professionalism" may be eroding more rapidly than one would like to admit. Entrepreneurism may be just one small nail in a rapidly closing coffin. Whether it should be a major focus of attention is unclear. If patients choose physicians because they are in their "book or plan" or if patients are unwilling to tell their physicians confidential information because their medical records will be reviewed by multiple third parties, what will be the effect on the "profession?"

Whether physicians will be able to maintain their "professionalism" in the present climate is difficult to predict. I am not convinced that physicians should be brought to task for their involvement in out-patient facilities without first looking at the total environment which has fostered such behavior. Haphazard and piecemeal attempts to repair a leaky roof usually fail. What we need is a new structure that has a solid foundation. The questions regarding "entrepreneurism" and "professionalism" just point out the inadequacies of our current system.

Marshall B. Block, M.D.
Editor

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In This Issue:

- The Current Status of Cardiac Electrophysiology
- Stop Disability Insurance Rates From Increasing Now
- Physicians in the News
- New Members
- The Practice Management Corner: CPT-4 Coding
- Letters to the Editor
- Classified Ads

From Our President

Mark Ivey, Jr., M.D.

Yesterday, an elderly rancher lady came into my office from Punkin Center with a chief complaint of some blood in her stool. After doing the proper functional inquiry, physical exam and already aware of her family history, personal history and past medical history, I decided it would be helpful to do some x-rays and endoscopy. Knowing that she would need pre-certification, I asked my office staff to make the proper arrangements for an admission to our little hospital, including notifying her insurance company.

I'm not naive about the system that has been imposed upon us; so, when the clerk in Chicago told my front office that Mrs. Jones didn't appear to her to be in acute distress and should have "all these tests" done as an outpatient, I decided to get on the phone. After explaining to the clerk that my little old lady lived by herself, across the Tonto River, where there is no bridge, the clerk informed me that the insurance company was not really interested in where she lived, but had a set of criteria that needed to be met prior to authorizing admission. I asked this "gatekeeper" if I could please talk with the physician in charge. I was put on hold for what seemed like an eternity when she finally informed me of the fact that the physician in charge was tied up, but would get back with me. "Could I have your number please?" I gave her my number and went back in to see my patient.

Mrs. Jones in her western drawl asked, "What seems to be the problem sonny, I've got Medicare, and they'll take care of it won't they?" I wanted to really tell her what I thought of the system, but then I didn't want her to be upset and after all it wasn't her fault or . . . was it?

No, it wasn't either Mrs. Jones or Dr. Ivey who created this system. It was *all* of the Mrs. Joneses and the Dr. Iveys who either expected the politicians, lawyers and insurance companies to take care of them or who didn't stand up together and protest loudly enough when the system imposed itself.

A significant majority of physicians failed to join together on behalf of their patients, and also failed to enlist the political support of their patients.

And because there wasn't enough of a unified effort by physicians *and* their patients, the bureaucrats who consider cost controls more important than people took control of patient care.

But it's not too late. All of us know colleagues who are among the unrecruited. To them we must have only one thing to say:

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MICA has filed a Reduced Tail Premium Program with the Arizona Department of Insurance. If approved, this new program will reduce our current policyholders' tail premiums by 5% for each consecutive year of qualifying coverage – up to a 50% reduction.

Once this program is in effect all full coverage years after your current MICA retroactive date will be counted. So if you've been covered by MICA for five such years, you have already accumulated a 25% tail reduction.

No other carrier in Arizona is offering these reductions. MICA's unique program has no age limitation and does not require retirement from practice.

Tail coverage, or "extended reporting endorsement," is necessary to protect you from occurrences that are not discovered or reported until after your policy has expired. As a doctor-owned carrier, insuring more Arizona physicians than any other company, MICA wants to make this essential coverage less costly and less restrictive for our policyholders.

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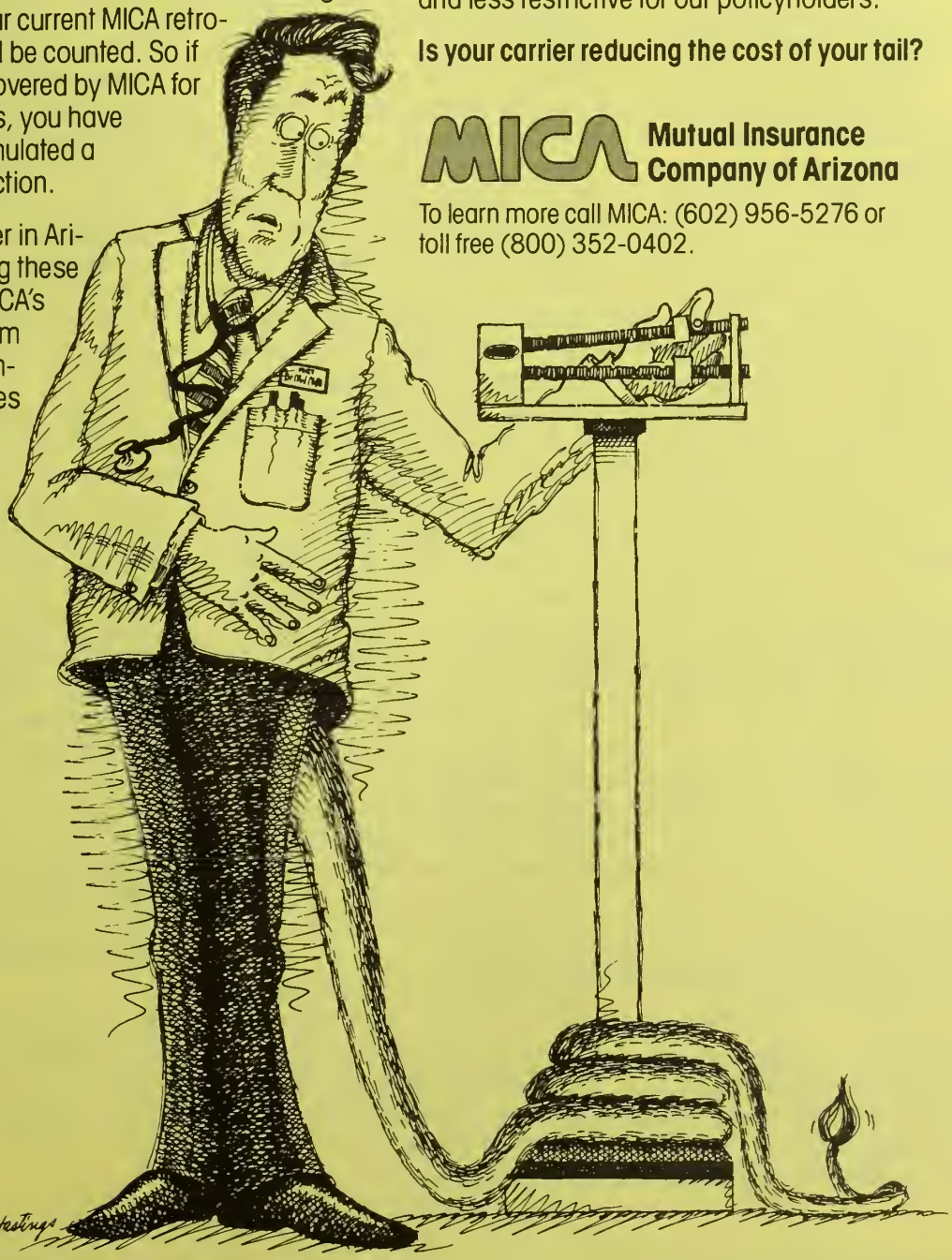

The Current Status of Cardiac Electrophysiology

Cardiac electrophysiology is the study and analysis of internal and external recordings of cardiac electrical activity as applied to the diagnosis and therapy of cardiac dysrhythmias. The understanding of cardiac electrical responses to programmed atrial and ventricular stimulation is integral to these studies.

The performance of a clinical cardiac electrophysiologic study requires the insertion of electrode catheters through the venous and/or arterial system to record and stimulate electrical activity in the intracardiac chambers, or occasionally the coronary sinus, pulmonary artery or aorta. Appropriately trained personnel and support staff, electrocardiographic and electrographic signal recorders, fluoroscopy, and a defibrillator and programmable stimulator are typically required. These components assure the patient's safety during the study.

Diagnostic electrophysiologic studies have been used to evaluate sinus node function, atrioventricular conduction, the His-Purkinje system and mechanisms of supraventricular and ventricular tachyarrhythmias. In particular, endocardial activation mapping techniques have improved the understanding of the mechanisms responsible for sustained ventricular tachycardia and the pre-excitation syndromes, most notably the Wolff Parkinson White syndrome, and allowed for therapeutic advances for these dysrhythmias.

Electrophysiologic studies are of use in selecting and evaluating the three main types of anti-arrhythmic treatment, namely pharmacologic, surgical and electrical therapy. Serial electrophysiologic studies to guide antiarrhythmic drug therapy for patients with recurrent sustained ventricular tachycardia, are superior to an empiric approach to drug selection. In patients with supraventricular arrhythmias or accessory pathways, in whom drug therapy is ineffective or not tolerated, surgical procedures for the destruction, isolation or division of the specific arrhythmogenic substrate are available; these offer the promise of cure of the arrhythmia for the patient. Pre-operative electrophysiologic study is important in characterizing the substrate of supraventricular arrhythmias, both anatomically and functionally. Similarly, pre-operative endocardial activation mapping during sustained ventricular tachycardia is crucial to planning surgical approaches to this problem.

The automatic implantable cardioverter-defibrillator (AICD) is to be considered in the treatment of patients resuscitated from ventricular fibrillation or hypotensive episodes of sustained ventricular tachycardia (in the absence of acute myocardial infarction or a treatable cause), in patients with unexplained syncope and inducible ventricular tachyarrhythmias, and possibly in patients surviving aborted sudden cardiac death without inducible ventricular tachyarrhthmia. Electrophysiologic study will aid in establishing the applicability of the device and its efficacy and safety in a particular patient.

Interventional electrophysiology aims at interrupting or destroying the specific cardiac tissue responsible for the genesis or maintenance of an arrhythmia. Techniques being investigated include catheter mediated ablation and intentional coronary arterial occlusion. These methods depend on accurate endocardial activation mapping of the arrhythmogenic tissue.

In patients with these serious arrhythmias, electrophysiologic studies provide diagnostic and prognostic information, provide support for catheter mediated or surgical ablation of arrhythmogenic tissue, and aid in assessing the suitability of anti-tachyarrhthmia devices.

Lionel Faitelson, M.D.
Assistant Professor of Medicine
Section of Cardiology
College of Medicine

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A sensible financial plan is one that eliminates taxes on your investment income--rather than just deferring taxes to a future time.

The equivalent yield table below illustrates the benefits of double tax exemption for individuals under 1988 federal tax rates and under current state tax rates. Locate your income tax bracket (after deductions and exemptions) and read across to see the approximate taxable yield needed to match the tax-free return of a **NUVEEN ARIZONA TRUST.**

For example, with joint taxable income of $29,800 to $71,900, you would be in the 32% combined federal and Arizona tax bracket and would need a taxable investment paying 10.66% to equal a tax-free return of 7.25%.

1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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Stop Disability Insurance Rates From Increasing Now!

If you could buy a health insurance policy that would lock in your current insurance rates until age 65 you would consider yourself incredibly fortunate wouldn't you? You bet you would! You would take action to buy a policy like that immediately!

Well, guaranteed renewable, noncancelable disability income insurance is a fixed rate type of health insurance that can't be canceled. It has been around for a long time and it does lock in rates. It is issued by the strongest and safest insurance companies in the industry. However, the rates on this type of insurance are rising rapidly. It is likely they will continue to increase (remember already issued guaranteed renewable, noncancelable policies have fixed constant rates). Some commentators are even starting to wonder if fixed rate policies will continue to be issued in the future.

Why the sudden concern by the disability carriers? Well, it's pretty simple. For years disability claims were reasonably predictable. Insurance companies could issue policies with fixed rates and know with reasonable certainty they could cover the risk. Disability carriers are now seeing large increases in claims not previously experienced. Many disability companies are losing money. While people are living longer because of medical science, many of those people whose lives are being extended are not able to work. So life insurance claims go down and disability claims go up. Also, people are claiming stress related disability at ever increasing numbers. With modern medical treatment, people with cancer, AIDS, heart problems, etc. might live 6, 12, or 24 months longer than they used to. At $1,000 to $20,000 a month in benefit claims, costs accelerate quickly!

If you have no current coverage, you need more coverage, or your disability income policy can increase your rates, it is important for you to consider buying a fixed rate type of disability coverage now. This is true for two important reasons. First, as you get older the rates increase because your health risk increases. Secondly, as I stated before, rates are going up because of increasing claims caused by sick people being sustained longer.

Description	Age	Person Age 40 Waits 2 Years to Buy Policy	Age	Person Age 50 Waits 2 Years to Buy Policy
1989 Rate, Age...	40	$2,120.75	50	$3,402.12
1987 Rate, Age...	40	(1,977.53)	50	(2,918.48)
Policy Rate Increase (A)		143.22		483.64
1989 Rate, Age...	42	2,327.30	52	3,681.35
1989 Rate, Age...	40	(2,120.75)	50	(3,402.12)
Rate Increase Due to Age Increase (B)		$206.55		$279.23
Total Increase In Insurance Cost Due to Delay (Line (A) + (B)		$349.77 Per Year		$762.87 Per Year

The above illustration demonstrates just how much a 40- and 50-year-old person's annual rates would have increased by procrastinating over the last 2 years. The illustrated coverage provides $5,000 per month in disability benefits. The benefits continue until age 65. The policy holder waits 60 days before benefits begin:

Age 40 —Total cost of procrastinating 2 years = $349.77 per year!

Age 42—Total additional cost to age 65 (23 years x $349.77) = $8,044.711!

Age 50 —Total cost of procrastinating 2 years = $762.87 per year!

Age 52 —Total additional cost to age 65 (13 years x $762.87) = $9,917.311

Another point you should consider in purchasing a fixed rate type of policy is the strength of the company issuing your policy. The fixed rate is no good if the insurance company goes out of business. You would find yourself shopping for a new contract when rates might be much higher or you may then be uninsurable. So make sure you buy a policy with a strong company who is a leader in the disability area!

The main point I want you to act on is the urgency of locking in rates now. Just look at your health insurance, your auto insurance, your malpractice insurance and think how nice it would be if you could have locked them in 5 years ago!

For ArMA's members with health problems who are paying higher rates, cannot get coverage at all or who have waivers on their coverage, ArMA has good news for you! We have negotiated with our carrier to issue you as much as a $2,000 a month, to age 65, standard fixed rate type policy. The only exceptions to anybody being issued this policy are:

- You cannot have AIDS.
- You must be working.
- You cannot be claiming disability benefits when you apply.
- You cannot own a Monarch Life Insurance Co. disability contract, and
- You must be an ArMA member.

This is an incredible deal for those of you with health problems. The policy issued is the same contract that our healthy members are issued and the cost is at the same discounted rate! We can also offer our healthy members an easy hassle-free additional $2,000 a month benefit. No medical exams are required on this guaranteed policy. It's quick and easy!

Speaking of discounts, we have negotiated a 15% discount for all ArMA members. There is also an additional 10% discount for non-smokers. Be assured this policy is issued by an industry leader (A.M. Best's highest rating A + c (Superior) rated company). The contract terms are some of the best in the industry. For more information on a fixed rate type disability insurance policy, or ArMA's discounts, you may call your personal ArMA financial services representative, or Ken Davis if you don't already work with us, at ArMA Membership Benefits, Inc. at (602) 246-8986. Also, if you are wondering about the quality of your current policy we can tell you your insurance company's A.M Best rating. Or we can review your policy contract provisions for you at no charge.

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Physicians in the News

Robert M. Kershner, M.D., an ophthalmologic surgeon at Orange Grove Eye Surgery Center on the campus of Northwest Hospital in Tucson has performed the nation's first bifocal lens implant. Dr. Kershner said the process, unlike its predecessor, promises to provide clear vision both near and far without dependence on eye glasses. Previously, the lens implanted only allowed for one focus, usually for distance.

The operation was performed in August on the left eye of a 75-year-old Tucson woman who had cataracts in both eyes. Dr. Kershner had previously performed the traditional unifocal, or single vision, lens implant in her right eye.

This year marks the 40th anniversary of the first single-vision lens transplant. However, unlike the eye's natural lens, the unifocal implant cannot change focus and individuals still require eyeglass correction for either distance or near vision.

The new bifocal lens, developed by Pharmacia Ophthalmics, is made from a plastic-like material offering a lifespan as long as that of the patient who receives it.

"This is one of the greatest advances in intraocular surgery," Dr. Kershner said, but it is not one of those things that patients can call their doctor and arrange. He indicated the operation will instead be reserved for people who have lost their vision because of cataracts. The cost of the surgery is estimated by Dr. Kershner to cost "a couple of thousand dollars," with Medicare providing some reimbursement.

The results of bifocal lens implants performed in Tucson and around the country during the next few months will be studied and analyzed by the U.S. Food and Drug Administration before the lens is approved for use throughout the nation. The approval process is expected to take from 18 months to two years.

"This is the core investigation of the lens," Dr. Kershner said. For that reason, the number of patients will be limited before it will become available to the general public.

Dr. Kershner is a graduate of Boston University and the University of Vermont College of Medicine.He completed a residency in ophthalmology at the University of Arizona and was Chief Resident in ophthalmology at the University of Utah Medical Center in Salt Lake City.

He has written many scientific articles on the treatment of eye diseases, travels nationally lecturing to other ophthalmologists on microsurgical techniques and is an active member of the Arizona Medical Association, the Arizona Ophthalmological Society and American Society of Cataract and Refractive Surgery.

The shortage of surgical gloves which occurred with the advent of America's AIDS epidemic has led a Mesa gynecologist into an alternate business.

Steven M. Linnerson, M.D., along with a partner, makes latex examination gloves. The physicians developed the formula for the gloves as a result of Dr. Linnerson's chemistry background and personal determination to try alternatives until one worked.

The right stuff was finally discovered and the glovemaking business took off. Dr. Linnerson's shop will be turning out gloves 24-hours a day on two different machines when it is in full operation.

The machine that makes the gloves consists of about 2500 porcelain "hands" waving along a 200-foot length of the enormous machine that creates the latex into gloves. The hands take the gloves through a series of processes which include dipping and rinsing, drying and then another dipping. In the final stages, they are dipped in the latex vat, rotated to evenly distribute the coating and finally dried. One of the last processes is a dusting of corn starch to make them easy to put on.

A "zealous advocate for children's health," a "taskmaster in the classroom," and a "role model who reached out to bewildered students" are some of the ways alumni describe former UA College of Medicine Vice Dean **Vincent Fulginiti, M.D.**

After 20 years of service to the College of Medicine, Fulginiti resigned in April to become Dean of New Orleans' Tulane University medical school—one of the nation's oldest and largest.

Dr. Fulginiti founded the pediatrics department in 1969 and served as its chairman until 1985, when he became the college's second vice dean.

His legacy of achievement is extensive. By the time he left pediatrics, it was well on its way to a ranking in the top 25 percent of all U.S. pediatric departments.

As vice dean, he led the way in computerizing the college, equipping its first computer lab for students and revising curriculum to include more small-group instruction than ever before. He chaired a campuswide committee to ensure salary equity for women faculty, resulting in many positive changes in salary structures. And, during a critical time of transition for the College of Medicine (December 1987 to May 1988), he served as acting dean.

"We can talk at length about planning and buildings and improvements to the college, but I'm proudest of the people I've worked with," Dr. Fulginiti says.

"The fondest memories for me are with the first class of 32 students. All the faculty members worked toether with that class to make the College of Medi-

Continued on page 13

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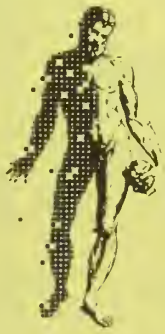

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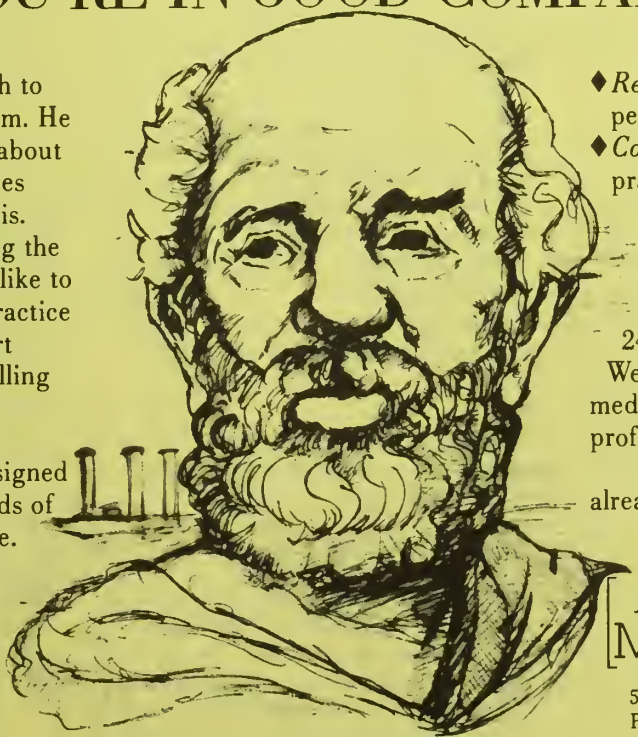

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State University of New York
College of Medicine
Syracuse - 1984

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Faculty of Medicine
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University of South Florida
College of Medicine - 1984

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State University of New York
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Georg August University - 1974

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Obstetrics & Gynecology
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John J. Swain, M.D.
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University of Arizona
College of Medicine - 1985

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Pulmonary Diseases
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Gujarat University - 1971

Resident

Maricopa

David G. Van de Wyngaerde, M.D.
Orthopedic Surgery
Maricopa Medical Center
Phoenix
University of Arizona
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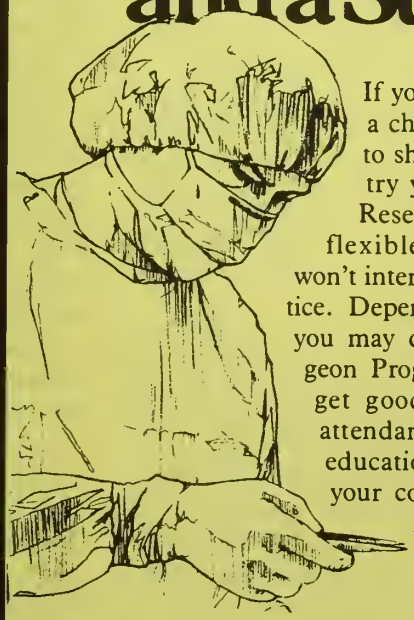

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The Practice Management Corner CPT-4 Coding

Introduction

With the support and enthusiasm of the Arizona Medical Association we are able to present a series of six articles which will address specific areas of CPT-4 coding: Medicare's national and local HCPCS coding, ICD-9-CM coding, and reimbursement issues.

Our main goal throughout these articles is to *stress the importance of physician and staff involvement* when dealing with CPT-4 coding and reimbursement for physicians' services. Through specific examples, these articles will help show you how to increase your practice revenue, improve patient and staff relations, effectively monitor your reimbursement, and prepare for audits.

The Origin of CPT-4

The introduction of the Physicians' Current Procedural Terminology, Fourth Edition (CPT-4) coding system in the early 1980s brought about a new way of coding for physicians services. The CPT-4 coding system, which replaced the Relative Value Studies (RVS), determines reimbursement based on the type of service and diagnosis rather than on the RVS unit value. This change in systems occurred not only to help contain costs but also to prevent abusive overcharging for services. Today, the CPT-4 coding system is the principal coding system recognized among insurance carriers. However, the Healthcare Financing Administration (HCFA) developed an additional coding system known as the HCFA Common Procedure Coding System (HCPCS). This system is divided into two levels, national and local, and was introduced to supplement the CPT-4 system. (We will discuss HCPCS coding in an upcoming issue.)

The Format of the CPT-4 Coding Book

The CPT-4 book is designed so that accessing a particular code is relatively easy. There are six main sections in the CPT-4 book, the first of which is a brief but informative introduction to its content. Thereafter, each section is classified by the type of service as follows:

Type of Service	Code Range
Medicine	90000-99199
Anesthesia	00100-01999
Surgery	10000-69979
Radiology	70010-79999
Pathology and Laboratory	80002-89399

Familiarity with your range of codes will help tremendously when referencing your specialty area. Since there are approximately 7,000 CPT-4 codes, knowing that your codes begin at 30000, for example, will save you valuable time. However, it is just as important to be familiar with all areas of the CPT-4 book so that you do not become "locked in" to one group of codes. By expanding your knowledge in all areas of the CPT-4 book you will be better able to choose the most accurate, not just the most convenient code.

Steps To Take Prior To the Final CPT-4 Code Selection

In order to properly code a procedure, a thorough review of the operative note or chart note is recommended prior to the final CPT-4 code selection.

When reviewing the notes look for unusual, complex, prolonged, or extreme conditions and multiple diagnoses which may affect choosing the most accurate CPT-4 code. While reviewing the notes you should also look for proper documentation to support the level of service. This is especially true of physician visits and consults because of the number of levels of service from which to choose. For example, the chart note "patient seen and examined" may not provide enough information to constitute more than a minimal office visit. There is clearly a need for additional documentation relating to the care of the patient if higher levels of service are to be used.

Once the operative or chart notes have been reviewed, you are ready to choose the CPT-4 code!

How To Quickly Choose the Most Accurate CPT-4 Code

Look in the CPT-4 Index! Looking up the service in the CPT-4 index

will save time usually spent thumbing through each section of the book searching for the right CPT-4 code.

However, even though the CPT-4 index may provide you with a code for your service, you should always cross-reference the code. Cross-referencing with either the national or local HCPCS is always recommended. But first, you should cross-reference the CPT-4 code with the range of codes specified in the CPT-4 index for your procedure. For example, the CPT-4 index directs you to use codes ranging from 17000 to 17010 for the destruction of facial lesions. In order to locate the most accurate code, you must look under that range of codes within the corresponding section of the book to find the one that best describes your surgical procedure. Also, the CPT-4 index does not indicate whether the surgical procedure is a starred (*) procedure or if the description has been revised, added or deleted from the previous year. That information can also be obtained by looking at the range of codes within the corresponding section of the book.

Reimbursement Based On the CPT-4 Code Submitted

The expression "An incorrect code is paid incorrectly" is best demonstrated by the following example. You may lose revenue if you submit CPT-4 code 17000*, instead of 17010, for the complicated destruction of a facial lesion. Reimbursement from the Industrial Commission of Arizona (Workers Compensation) is $45.42 for 17000* and $89.55 for 17010, creating a potential of $44.13 in lost revenue for you if the charge is coded incorrectly.

The insurance carrier will pay according to the charge submitted, so it is *up to the physician to code the service as accurately as possible.*

How Understanding the CPT-4 Book Can Help You Accurately Code Your Services and Prepare You For An Audit

If the physician understands the content of the CPT-4 book, he or she is more likely to choose accurate CPT-4 codes.

For example, the CPT-4 code 17000* is to be used for the destruction of one facial lesion and code 17001 is for the destruction of the second and third lesions. If a physician is unaware of this distinction and uses the CPT-4 code 17000* for his second and third lesions, the charges will have been coded incorrectly.

In addition, the physician who understands both the format and content of the CPT-4 book takes less time to find the best code for his or her service. Subsequently, the physician is less likely to become impatient and choose the incorrect code.

In an audit situation, services found to be coded incorrectly may be subject to further review by the insurance carrier. Also, the physician may suffer civil and/or monetary penalties if services have been reimbursed based on incorrect codes. If, after an audit, it is determined that services reimbursed by the insurance carrier were paid based on incorrect codes, the physician may have to reimburse both the insurance carrier and the patient(s) for any amount overcharged.

By understanding and using the resources available in the CPT-4 book you can greatly reduce the risk of submitting incorrect codes and be better prepared for an audit.

Summary

Words of caution: The physician should always be the one responsible for coding his or her services. However, we recommend that the physician consult the billing staff or office manager for any input they may have regarding the determination of the CPT-4 code.

With all of the ongoing changes in reimbursement for physicians' charges, keeping up with the basic skills we have mentioned today can make a noticeable difference in the effectiveness of your practice. Becoming "CPT-4 literate" will enhance your ability to operate your practice at its optimum level.

Claire Miller and Joan Miller are President and Chief Financial Officer of SysteMedical Management, Inc., a medical practice firm located in Mesa, Arizona. They can be reached at (602) 833-4855

Dr. Fulginiti

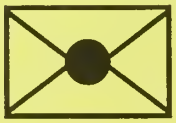
Continued from page 8

cine a functioning reality. Students came to our house at the end of each clerkship for a beer-and-hamburger type party on the patio. We knew them as well as they knew us. They knew our children, they knew our spouses, and ... many of those students have remained very good friends over the years."

One of Dr. Fulginiti's college classmates, George Comerci, M.D., of the Pediatrics Department, says, "I've known Vince since 1957, longer than he's known his wife. I have watched him develop in every phase of his career. He is a born leader, brutally honest, with a tremendous gift to nurture people—that's what being an administrator is all about."

Nowhere is this gift of nurturing more evident than in the pediatricians Fulginiti recruited and trained. He helped launch many successful careers from the department, including those of three pediatric department heads across the country. ■

Letters to the Editor



Advice From Dr. Truth:

Q "How can I get my radiologist to still respect me in the morning?"

A. Four simple ways to enhance a clinician's respect in the eyes of a radiologist are far too often overlooked. Let me share these with you.

1. Keep it simple

When ordering studies of the cervical or lumbar spine, the standard three views are usually adequate for initial evaluations or for follow-up after a diagnosis has been made. Oblique views are seldom needed in a primary care setting. Leave those extra views to the specialists. Likewise, the studies of the knee which some clinicians order routinely to include standing views, tunnel views and sunrise views. All of these special views have their usefulness, but in first encounters the yield is vanishingly small. Stick to basics.

2. Do it twice

A KUB is frequently ordered inappropriately. It is most useful as a plain film evaluation of kidneys, ureters and bladder, especially when seeking evidence of radiopaque urinary tract stones. It is a single supine film. On the other hand when dealing with a suspected acute abdomen due to non-urinary tract causes, supine and upright films are necessary in order to show air/fluid levels, localization of gaseous distension and free air. The supine and upright films are often accompanied by a chest x-ray, since chest disease can give abdominal symptoms and because patients with serious abdominal symptoms often are admitted to the hospital. The combination of the three studies is often simply called an acute abdomen study at many institutions but this varies.

3. Ask how it was for the other person

Most often when copies of old x-ray studies are requested, no request is made for the interpretation. Somehow the custom has evolved of sending the films without the interpretation unless specifically asked for. The local radiologist is then usually asked to study the films and render an opinion. Often this can be a time-consuming affair, especially in a patient with a thick file of films from chronic or multiple illnesses. If you ask for the reports and send the patient's signed consent, duplicate effort can be avoided.

4. Communicate

Have you ever read an article of this type that did not mention communication? It cannot be overstressed. We can help you, but we must know what you want; tell us. Pick up the phone or stop into the department. We know the available modalities; that's our job. We can save your patient expense, delay and unnecessary radiation if you consult us with your diagnostic problems. Like anyone else, we love to give advice and will extend ourselves to do so. We're all in this together and have a common goal -- the welfare of the patient. If you keep these four tips in mind, I promise you that radiologists will do their best to make the earth move for you.

Edward H. Kolner, M.D.

Gleanings from the Minute Book

By Dry Gulch Jake

Now that this prestigious society, ArMA, is approaching the century mark, 1892 - 1992, you may be interested in some events along the way.

At the 1911 Annual Meeting, W. Warner Watkins, M.D., of Phoenix, introduced the following resolution, "by request."

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The minute book notes continue, after quite a spirited discussion it was moved, "that the question be submitted to a referendum of the members of the Association." Perusal of the minutes of subsequent meetings fails to make further reference to this subject.

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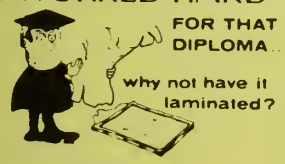

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Clinical Investigation

Biweekly Intracavernous Administration of Papaverine for Erectile Dysfunction

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To determine the efficacy of the intracavernous administration of papaverine hydrochloride every 2 weeks to treat male impotence, we recruited 50 patients from a sexual dysfunction clinic. Of these, 8 did not complete the course of papaverine therapy. A total of 8 had complications, including priapism in 3 and ecchymoses or urethral bleeding in 5. In 30 patients who had substantial vasculogenic disease, there was a notable improvement in the penile blood pressure after papaverine treatment, although only 9 reported successful sexual intercourse. The penile blood pressure in the remaining 12 patients without substantial vascular disease increased modestly after therapy, and 5 persons reported satisfactory sexual activity. We conclude that administering papaverine intracavernosally every 2 weeks improves sexual potency in a subset of sexually impotent patients. Those with severe vasculogenic disease and a penile-brachial pressure index of less than 0.65 are not good candidates for this regimen.

(Mooradian AD, Morley JE, Kaiser FE, et al: Biweekly intracavernous administration of papaverine for erectile dysfunction. West J Med 1989 Nov; 151:515-517)

Although psychological factors often complicate sexual dysfunction in men older than 40 years, the underlying primary cause is usually organic.[1-4] The predominant organic cause of impotence is vascular disease. The primary defect in vasculogenic impotence is impaired maximal penile blood flow, although the ultimate common denominator of erectile dysfunction of various causes is a failure of the accumulation of blood in the corpora cavernosa, hence, the rationale of using vasodilating agents such as papaverine hydrochloride and phentolamine hydrochloride in treating vasculogenic impotence.[5-7] It has been suggested that patients with vasculogenic impotence who respond to papaverine should be offered training in self-injection.[7,8] The long-term effects, however, of intracavernous injections remain unknown, and possible scarring of the spongy tissue is of concern. It is thus of interest to determine the efficacy of alternate protocols of papaverine therapy given for a short period of time. We elected to determine whether the biweekly (once every two weeks) intracavernous administration of papaverine for a total of eight weeks would result in a persistent improvement of sexual potency in a subset of patients. It has been suggested that this regimen is an acceptable alternative to the autoinjection protocols.[9] We also tried to ascertain whether the clinical response—improved sexual potency—correlates with the improvement in penile blood flow.

Patients and Methods

A total of 50 patients were recruited from the sexual dysfunction clinic at the Sepulveda (California) Veterans Administration Medical Center. The mean age was 59.2 ± 1.6 years, with a range of 40 to 70 years. Patients were excluded who did not have a sexual partner or who had strong psychogenic diseases or androgen deficiency without testosterone replacement. All subjects signed a consent form approved by the hospital's Human Subjects Study Committee. None of the patients had been previously treated for sexual dysfunction, except for four hypogonadal patients who were on testosterone replacement therapy. The sex partners of all patients were also interviewed. The mean duration of impotence (inability to have intercourse) was 4.25 ± 0.79 years (range 5 months to 16 years). Before the onset of sexual dysfunction, all patients had been engaged in healthy sexual activity. Eight did not complete the course of therapy either because of a complication or a lack of motivation. Of the 42 patients who completed therapy, 13 had diabetes mellitus, 8 were receiving treatment for hypertension, and 8 had stable coronary artery disease. Other medical problems included chronic obstructive lung disease in 4 patients, alcoholic neuropathy in 1, alcoholic cirrhosis in 1, and arthritis in 2. Five had no major medical problems. All except six of the patients were smokers with a history of more than ten pack-years.

The penile blood pressure was measured by Doppler ultrasound. We found the coefficient of variation of penile blood pressure measurements within the same person to be 3.1%. Patients were considered to have significant vasculogenic disease if the ratio of penile systolic pressure to brachial artery systolic pressure (penile-brachial pressure index) was less than 0.75 with the patient resting, standing, or exercising. The cause of the sexual dysfunction in the

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TABLE 1.—*Ratios of Penile Systolic Blood Pressure to Brachial Systolic Blood Pressure (Mean ± SEM) in Right and Left Dorsal Penile Arteries Before and After a Course of 4 Papaverine Hydrochloride Injections**

Patients	Before/After Injections	Penile-Brachial Pressure Indexes					
		Lying		Standing		Exercising	
		Right	Left	Right	Left	Right	Left
With vasculogenic impotence, n=30	After	0.79±0.02†	0.78±0.02†	0.79±0.03†	0.77±0.03†	0.72±0.03†	0.69±0.03†
	Before	0.70±0.02	0.68±0.03	0.65±0.04	0.65±0.04	0.58±0.02	0.57±0.03
Without vasculogenic impotence, n=12	After	0.88±0.05	0.93±0.04	0.88±0.03†	0.92±0.01†	0.82±0.04	0.86±0.04†
	Before	0.84±0.05	0.92±0.04	0.83±0.04	0.88±0.02	0.80±0.04	0.80±0.04

*There was no significant difference between the mean brachial systolic pressure measured before and after papaverine injections.
†Significant difference compared with measurements taken before papaverine given, $P<.01$.

study group (n = 42) was considered predominantly vasculogenic in 30 persons based on penile blood pressure measurements. Of these, eight had the pelvic steal syndrome (defined as an exercise-induced reduction of the penile-brachial index by greater than 0.15),[10] and four patients were hypogonadal on testosterone replacement. In 12 patients the cause was multifactorial, and the penile-brachial pressure indexes were greater than 0.75.

The patients were asked to discontinue nonsteroidal anti-inflammatory agents before the papaverine trial. With a 27-gauge needle, papaverine hydrochloride, 60 mg in 5 ml of normal saline for a total 7 ml, was administered immediately distal to a rubber band firmly applied at the base of the penis. The passage of the needle through the fibrous envelope could be felt, and appreciable resistance to the forward flow of the injectant was noted. On injection, the patients complained of a moderate burning sensation that lasted 30 to 60 seconds. After the penis was massaged gently for two minutes, the rubber band was cut and the patient was asked to stand up for seven minutes. At the end of seven minutes, the immediate response was assessed subjectively by the physician as a percentage of a normal erection. The patients were advised to refrain from sexual activity for 24 hours after each injection to reduce the risk of priapism. The papaverine was administered every two weeks for a total of four injections. The interval sexual function was evaluated during each visit. The criteria for successful therapy included patient satisfaction and the ability to perform coitus during more than 50% of trials, at least once in the interval between injections, and for the two weeks after the fourth injection. The penile blood pressure was measured five days after the last dose of papaverine. The results are shown as a mean ± SEM. The statistical analysis was carried out by a one-way analysis of variance and the Student's *t* test for paired variables.

Results

The erectile response immediately after the papaverine was administered was substantially superior in those with a penile-brachial index of greater than 0.75 compared with those having lower values. In this group, 11 of 12 men had an immediate erection equal to or greater than 80% of a normal one as assessed by the examining physician. In the group with vasculogenic disease as determined by penile-brachial pressure indexes, only 9 of 30 men had an immediate erectile response of 80% normal. The immediate response appeared to be modestly improved with repeated injections. Because of the subjective nature of the assessment, however, the significance of this observation could not be ascertained. The immediate response lasted as long as two hours.

Table 1 shows that in patients with vasculogenic disease, papaverine therapy considerably improved the penile blood pressure measured in the two penile arteries at three different positions. Patients with nonvasculogenic impotence showed a modest improvement in penile blood pressure in one artery while standing or exercising. There was no significant difference between the mean brachial systolic pressure measured before and after papaverine was administered. The papaverine therapy was successful in permitting coitus with ejaculation in 9 of 30 men with substantial vasculogenic disease and in 5 of 12 with normal penile blood flow. Of the eight patients with "pelvic steal," two had improved sexual potency, although the penile blood pressure measurements improved more than 15% above baseline both at rest and after exercise in all eight patients. There was no correlation between the immediate response and the outcome of therapy. Only one of the men who had a penile-brachial pressure index of less than 0.65 (n=12) had a clinical response to papaverine therapy. Of the 14 patients who responded to papaverine therapy, 5 were still having satisfactory coitus six months after the last dose of papaverine. All these patients were considered to have normal penile blood pressures based on the Doppler measurements after papaverine treatment. None of the eight men who discontinued papaverine therapy before the third dose reported an improvement in sexual function.

There was no correlation between the clinical response to therapy and improved penile blood pressure measurements when all the patients were considered. In the group with vasculogenic impotence, however, those who showed clinical response had higher penile blood pressure measurements at baseline and after papaverine injections than those who did not respond (Table 2).

There were few complications. In three patients, priapism developed after the first injection, necessitating the aspiration of blood from the cavernosa. All three had normal penile-brachial blood pressure indexes. The priapism developed within six to eight hours after the injection when a patient attempted to have sexual intercourse. Five injections resulted in ecchymoses at the injection site, and, of these, two patients had a single episode of urethral bleeding without sequelae.

Discussion

Recently it was suggested that administering papaverine intracavernosally every two weeks for a total of eight weeks could be an acceptable alternative to the autoinjection protocols.[9(p162)] In our investigation a course of intracavernous papaverine did indeed provide substantial relief of sexual dysfunction in 14 of 42 patients studied. In five patients, substantial relief was reported after six months of papaverine

TABLE 2.—*Penile-Brachial Pressure Indexes in Patients With Vasculogenic Impotence Who Reported Clinical Response (Responders) and Those Who Did Not Respond (Nonresponders) to Papaverine*

Patients	Before/After Injections	Penile-Brachial Pressure Indexes*					
		Lying		Standing		Exercising	
		Right	Left	Right	Left	Right	Left
Responders, n=9	After	0.77±0.03	0.83±0.02	0.77±0.02	0.84±0.02	0.77±0.02	0.83±0.03
	Before	0.67±0.03	0.73±0.04	0.63±0.03	0.69±0.03	0.68±0.03	0.70±0.03
Nonresponders, n=21	After	0.79±0.02	0.75±0.03†	0.79±0.03	0.74±0.04†	0.67±0.03‡	0.62±0.03‡
	Before	0.70±0.02	0.66±0.03	0.65±0.05	0.63±0.04	0.55±0.03‡	0.51±0.03‡

*Mean ± SEM.
†$P<.05$ compared with responders.
‡$P<.01$ compared with responders.

treatment. Papaverine therapy was also beneficial in a subset of patients who were found to have normal penile blood pressures. The crude estimates provided by penile Doppler studies may have failed to define significant vasculogenic disease in these patients. In those with vasculogenic disease, papaverine therapy consistently improved the penile blood pressure measurements when patients were resting, standing, and exercising. In those with nonvasculogenic impotence, some improvement in penile blood pressure was observed in the standing or exercising measurements. The favorable response seen in patients with normal penile blood pressure measurements, however, could also be due to a "cure" of performance anxiety.[11] Although patients with severe impairment in penile blood pressure (a penile-brachial index of less than 0.65) are unlikely to respond to this regimen of papaverine therapy, for most patients or those with only mild vascular disease, the penile Doppler measurements either at baseline or after papaverine treatment do not predict the clinical response. Even for the eight patients with the pelvic steal syndrome, papaverine therapy was successful in only two who had an increase of greater than 0.25 in the penile-brachial index measured during exercise. It is noteworthy that in the group with vasculogenic impotence, those who responded to the papaverine trial had higher penile-brachial pressure indexes during exercise than did nonresponders, suggesting that the responders had less impairment in their penile blood flow. It appears that a major improvement in penile blood pressure may predict the clinical outcome, but modest improvements in the penile blood pressure are clinically insignificant. In the group with vasculogenic impotence, however, the most appropriate candidates were those with penile-brachial indexes in the range of 0.65 to 0.75. All except one of those with clinical response had indexes of greater than 0.65. Possible explanations for the failure of therapy in those with increased arterial flow include an inadequate brachial or penile blood pressure measurement, a venous leak, or a psychogenic component of sexual dysfunction. Of interest is that the immediate (seven-minute) erectile response to the administration of papaverine, although assessed subjectively, correlated well with penile blood flow measurements. An erection of 80% or more of normal was achieved by all but one patient who had a penile-brachial index of greater than 0.75; whereas, in those subjects with vasculogenic disease only, 9 of 30 patients had an erection of 80% or more of normal. These results suggest that patients with a severe vasculogenic component are less likely to respond to papaverine therapy.

Although the complication rate was high (8 of 184 injections in 50 patients), only priapism was considered a sufficient reason to discontinue the therapeutic trial in three persons. The other complications, such as bruising at the injection site or urethral bleeding, were accepted by three patients as minor problems, but two others who were not motivated and had a psychological component to their impotence elected to discontinue the trial. It is noteworthy that priapism occurred only in patients with normal penile blood pressures.

Overall, our data suggest that administering papaverine every two weeks in the cavernosa improves sexual potency in a subgroup of patients with a normal penile blood pressure or mild vasculogenic disease. It significantly improves the blood pressure measurements in almost all patients with vascular disease. Those who have penile-brachial pressure indexes of greater than 0.65 should be given a trial of biweekly papaverine injections. In some patients the clinical response may last for at least six months after the course of therapy. Future studies should be designed to evaluate the role of the present regimen of papaverine administration in a double-blind crossover fashion using saline injections as a control.

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Clinical Medicine

Blastocystis hominis—A Potential Intestinal Pathogen

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The parasite Blastocystis hominis *has been found in 10% to 18% of stool specimens submitted to microbiology laboratories. Controversy exists as to whether this organism can cause illness in humans. We have reviewed the records of 65 symptomatic patients with* B hominis *in their stool. We conclude that* B hominis *is a potential pathogen that may or may not require drug therapy depending on the overall clinical circumstances, the severity of symptoms, and the presence of other pathogenic organisms.*

(Babb RR, Wagener S: *Blastocystis hominis*—A potential intestinal pathogen. West J Med 1989 Nov; 151:518-519)

As noted by Zierdt, the history of *Blastocystis hominis* "is one of beguiling contradiction."[1] After being named in 1912, this organism was considered a harmless yeast until being reclassified in 1976 as a protozoan on the basis of structural and physiologic characteristics.[1] Whether *B hominis* can cause disease in humans remains controversial. Most authors think it is potentially pathogenic when present in large numbers in the intestine and when other infectious organisms are absent.[1-9] Others suggest that *B hominis* is not the cause of clinical illness but rather a harmless parasite in patients with gastrointestinal symptoms from other causes.[10]

Because *B hominis* can be found in 10% to 18% of stool specimens submitted to microbiology laboratories,[1,2,8] correlating its presence with patients' symptoms is important. We have therefore reviewed our experience at the Palo Alto Medical Clinic in an attempt to decide whether *B hominis* is pathogenic.

Methods

Over a 12-month period (August 1987 to August 1988) 2,700 patients submitted stool specimens for ova and parasite examination to the Palo Alto Medical Clinic microbiology laboratory. These unpurged specimens had been collected either at home or in a clinic office and were preserved in polyvinyl alcohol. They were subsequently centrifuged; the sediment was placed onto a slide, dried at room temperature overnight, and then stained with trichrome. All slides were examined under a microscope by licensed microbiology technologists. (The number of organisms present per microscopic field was not reported.) A total of 76 adult patients (3%) had slides positive for *B hominis* (Figure 1). The medical records of these 76 patients were then analyzed for clinical patterns associated with a stool specimen positive for *B hominis.*

Results

Of the 76 patients with a stool specimen positive for *B hominis,* the medical records of 11 did not contain relevant clinical information; thus, 65 records were available for review.

In all, 41 patients submitted at least three stool specimens. *B hominis* was found in all three specimens in 9 patients, in two of three specimens in 10 patients, and in only one in 20 patients. In one patient, the parasite was seen in four of six specimens, and in another, in one of five specimens. As shown in Table 1, other pathogenic parasites such as *Giardia lamblia, Entamoeba histolytica,* and *Dientamoeba fragilis* were seen in 19 patients, or about a third. Only two patients had cultures of stool specimens for pathogenic bacteria, and both were negative. Viral studies and stool smears for leukocytes were not done.

The records were scanty concerning possible predisposing factors for *B hominis* infection. A majority of patients (43) had traveled outside the United States, usually to Mexico, Africa, or Southeast Asia, within a few months of becoming ill. No one was identified as chronically ill or immunocompromised. One patient was noted as homosexual. Everyone was symptomatic, and most complained of diarrhea and abdominal pain. There was no mention of fever, chills, anorexia, nausea, or blood in the stool. None of our patients were evaluated with sigmoidoscopy or colonoscopy.

In all, 33 patients, including 4 with other parasites, were not treated. Subsequent clinic visits or phone calls indicated that 27 were well. The status of the other six could not be judged from available records. A total of 32 patients, including 16 with other parasites, were treated with metronidazole (Flagyl), and 28 became asymptomatic. Two patients felt no better when seen 12 months later. Two could not be traced. On the whole, those treated appeared more ill. One patient complained bitterly of long-standing diarrhea and rapidly responded to drug therapy. The follow-up was less than three months in most patients, and only seven had repeat stool examination for ova and parasites. Six patients (including three with other parasites) had been treated, and all six were negative for *B hominis.*

Discussion

Based on clinical experience in large medical centers and on isolated cases,[1-9] most authors think that *B hominis* can be pathogenic. Zierdt[1] and later Sheehan and co-workers[2] re-

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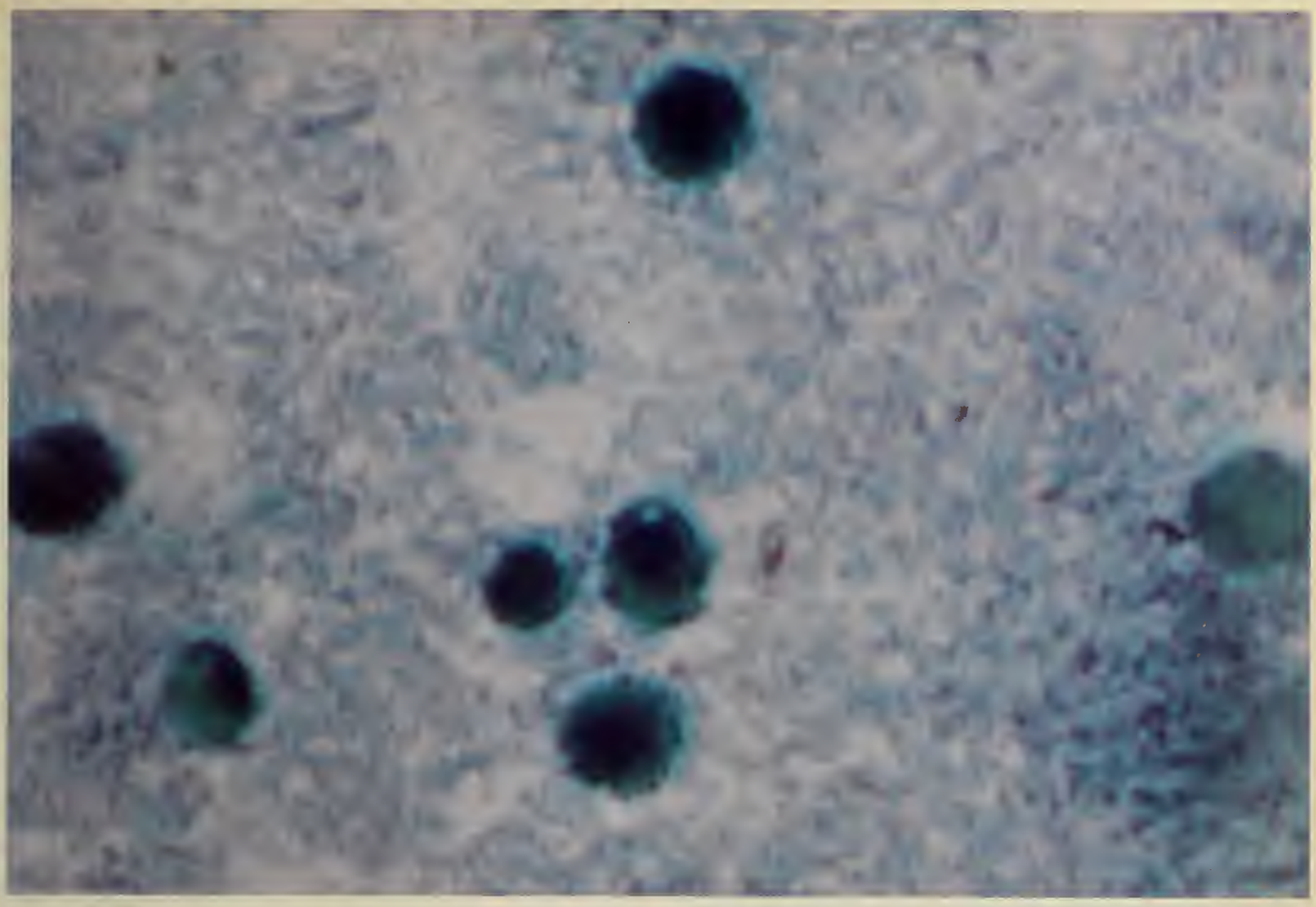

Figure 1.—The fecal smear shows *Blastocystis hominis* (trichrome stain × 1,000).

TABLE 1.—*Intestinal Parasites in Association With* Blastocystis hominis

Parasites	*No. of Patients*
Giardia lamblia	9
Dientamoeba fragilis	6
Entamoeba histolytica	4

port that large numbers of this parasite (greater than five per 40 × phase objective or oil-immersion microscopic field) in the intestinal tract often lead to abdominal complaints that respond to treatment. In two abstracts, one reviewing 15 patients and the other 32, it was concluded that *B hominis* could cause gastrointestinal illness.[8,9] Five recent case reports have described a total of six patients acutely ill with diarrhea.[3-7] All had *B hominis* only in their stool specimens, and each patient eventually responded to treatment with metronidazole or, in one case, with ketoconazole (Nizoral).[6]

In contrast, Markell and Udkow[10] have suggested that *B hominis* does not cause illness. They reviewed the clinical course of 148 patients with *B hominis* in their stool. A total of 116 had four or fewer stool examinations and were not studied further. Of the 148 patients, 32 had six stool examinations, all containing *B hominis;* in 27 patients, there were other pathogenic parasites as well. Appropriate drug therapy was given for the other parasites, and although these patients became asymptomatic, their stools continued to contain *B hominis.* Markell and Udkow think that successful treatment of a patient with *B hominis* represents the elimination of another perhaps undetected parasite or the alleviation of functional bowel symptoms with time alone.

On the basis of our experience and the literature reviewed above, we think *B hominis* is a potential pathogen that can in some patients lead to diarrhea and abdominal pain. A patient's overall health and the number of parasites in the gastrointestinal tract determine whether symptoms develop. Often, *B hominis* is an innocent bystander and not responsible for the patient's symptoms. Almost half of our study group became asymptomatic without treatment.

Prudent physicians will review the entire clinical findings before advising specific drug therapy for symptomatic patients with *B hominis* in their stool.

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Epiglottitis—An Increasing Problem for Adults

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In a 2-year period, 9 adults were admitted to hospital with acute epiglottitis confirmed by direct laryngoscopy or lateral neck radiograph, or both. The mean age was 53 ± 14 years, with acute epiglottitis occurring in 89% during the months of September to March. Intubation was required in 4 patients. The duration of symptoms was 7.8 ± 2.4 hours for intubated patients versus 18.8 ± 8.9 hours for those not intubated. For 6 patients an incorrect diagnosis was made on their first presentation. All 8 patients having laryngoscopy had typical findings, and none had respiratory obstruction precipitated by the procedure. In 5 patients blood cultures were positive, 4 for Hemophilus influenzae *type b, and 1 for* Streptococcus pneumoniae. *In 2 patients the* H influenzae *was ampicillin-resistant. All patients recovered after receiving parenteral steroid therapy and appropriate antibiotics.*

(Sheikh KH, Mostow SR: Epiglottitis—An increasing problem for adults. West J Med 1989 Nov; 151:520-524)

Epiglottitis, a disease primarily of children, was first described in an adult in 1936.[1] Recent reports suggest an increasing incidence in adult populations, but a large number of adult cases are misdiagnosed.[2-6] Our experience with nine cases of adult epiglottitis in 18 months prompts this report.

Methods

Between September 1983 and December 1985, nine cases of epiglottitis in adults were seen at Rose Medical Center, a 400-bed teaching hospital in Denver. The diagnosis was established by direct laryngoscopy or lateral neck soft tissue radiograph, or both. Pertinent clinical characteristics, bacteriologic findings, and outcome were noted for each patient.

A literature review identified additional case reports of acute epiglottitis in adults between 1965 and 1985, and data from these reports were grouped to determine incidence figures.

The *t* test was used for analyzing independent samples and the χ^2 test for association; all tests were two-tailed.

Results

Epidemiology and Clinical Characteristics

The clinical characteristics, bacteriologic findings, and outcome of our nine patients are shown in Table 1. The average age was 53 ± 14 years (range, 31 to 72); five were women. There was significant seasonality, with eight of nine patients being seen between September and March ($P < .01$). All patients had both sore throat and dysphagia on presentation, and three (33%) had temperatures greater than 38.5°C (101°F). Five patients (56%) presented with respiratory symptoms—dyspnea, stridor, drooling, the need to maintain an upright position—and four of these required an endotracheal tube. The mean duration of symptoms from their start to a correct diagnosis was 13.9 ± 8.7 hours. There was a significant shortening in the interval between the occurrence of symptoms and diagnosis in those patients requiring intubation versus those not requiring intubation (7.8 ± 2.4 hours versus 18.8 ± 8.9 hours; $P < .05$). Six of nine patients (67%) were initially seen by a physician and misdiagnosed, only to return on a subsequent visit with a progression of symptoms. In two cases, intubation was required on the second visit.

Diagnostic Procedures

No patient had respiratory obstruction precipitated by flexible laryngoscopy or neck radiograph. In Figure 1 the characteristic laryngoscopic findings of supraglottic inflammation and airway narrowing are shown for patient 6. The pretreatment lateral neck soft tissue radiograph from this patient is shown in Figure 2 and is notable for showing inflammation of the epiglottis, aryepiglottic folds, and the arytenoid cartilage. The inflammation had resolved after three weeks of treatment (Figure 3). All eight patients having laryngoscopy had characteristic findings. A falsely normal lateral neck radiograph was noted in one of nine cases.

Etiology

Blood cultures were done in all nine patients before antibiotics were administered. Five cultures (56%) were positive, four for type b *Hemophilus influenzae* and one for *Streptococcus pneumoniae.* Two of the four *H influenzae* isolates were ampicillin-resistant in vitro. Blood cultures in three of four patients requiring intubation grew pathogens. There was a trend towards a shortening of the duration of symptoms to the time of diagnosis in the five patients having positive blood cultures compared with the four patients with no-growth cultures (11.4 ± 5.4 hours versus 17.0 ± 11.8 hours), but this was not statistically significant.

Complications

Four patients had extraepiglottic complications. These consisted of pneumonia in three and empyema in two. In all

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TABLE 1.—*Adult Epiglottitis, Rose Medical Center Experience, Denver, September 1983 Through December 1985*

Patient	Date	Age, yr	Sex	Abnormal Laryngoscopy	Abnormal Neck Radiograph	Results of Blood Culture	Complications	Time to Diagnosis, hours	Missed Diagnosis 1st Visit
1	9/83	67	♂	Yes	Not done	*Streptococcus pneumoniae*	Pneumonia; intubated	8	Yes
2	9/83	64	♀	Yes	Yes	Negative	None	24	Yes
3	11/83	72	♀	Not done	Yes	*Hemophilus influenzae*	Empyema	20	Yes
4	1/84	50	♂	Yes	No	Negative	Intubated	6	No
5	4/84	31	♂	Yes	Yes	*H influenzae* (ampicillin resistant)	None	12	Yes
6	9/84	63	♀	Yes	Yes	Negative	None	8	Yes
7	9/84	42	♀	Yes	Yes	*H influenzae* (ampicillin resistant)	Pneumonia; empyema; intubated	6	No
8	1/85	54	♀	Yes	Yes	Negative	None	30	No
9	12/85	38	♂	Yes	Yes	*H influenzae*	Intubated; pneumonia	11	Yes

TABLE 2.—*Case Reviews of Adult Epiglottitis, 1965 Through 1983*

Institution (Reference Number)	Cases, Number	Survey Period	Years	Cases per Year
University Hospital of Wales, Cardiff (7)	9	1966-1976	10.0	0.9
Wayne State University, Detroit (8)	4	1977-1980	4.0	1.0
Strong Memorial Hospital, Rochester, NY (5)	10	1966-1975	9.0	1.1
University of Southern California, Los Angeles (9)	17	1963-1973	10.0	1.7
University of Chicago (10)	6	1979-1981	2.0	3.0
Gewtoffe Hospital, Hellerup, Denmark (4)	75	1965-1982	17.0	4.4
Michael Reese Hospital, Chicago (11)	3	1968	0.7	4.5
Harvard University, Boston (3)	75	1965-1981	16.0	4.7
Kaiser Medical Center, Denver (12)	5	1978	1.0	5.0
Institute of Medical Microbiology, Göteborg, Sweden (13)	10	1968-1969	1.5	6.7
Georgetown University, Washington, DC (14)	80	1975-1982	7.0	11.4
Northwestern University, Chicago (15)	15	1978-1979	1.3	12.0
Lahey Clinic, Boston (16)	3	1983	0.2	15.0

patients with pneumonia or empyema, or both, blood or pleural fluid cultures were positive for pathogens.

Treatment

Requiring intubation correlated with positive blood cultures, a rapid progression of symptoms, and the occurrence of respiratory tract symptoms. Intubation was done not prophylactically but, rather, if a patient's condition appeared to be declining or if respiratory symptoms were progressing. All patients received antibiotic treatment with either chloramphenicol or a β-lactamase-resistant cephalosporin. All patients also received parenteral corticosteroids (methylprednisolone sodium succinate, 125 to 250 mg every 6 hours) for 24 to 48 hours. All patients survived. The average duration of hospital stay was 5.3 days. The longest hospital stay was 18 days in patient 7, in whom *H influenzae* empyema developed.

Discussion

Incidence of Adult Epiglottitis

Cases described between 1965 and 1983 are presented in Table 2.[3-5,7-16] A substantial increase in the number of cases has occurred since 1976. Between 1958 and 1976, there were 69 cases of epiglottitis reported in adults, and from 1976 to 1983 a total of 203 adult cases were reported. An increased prevalence of other infectious illnesses caused by

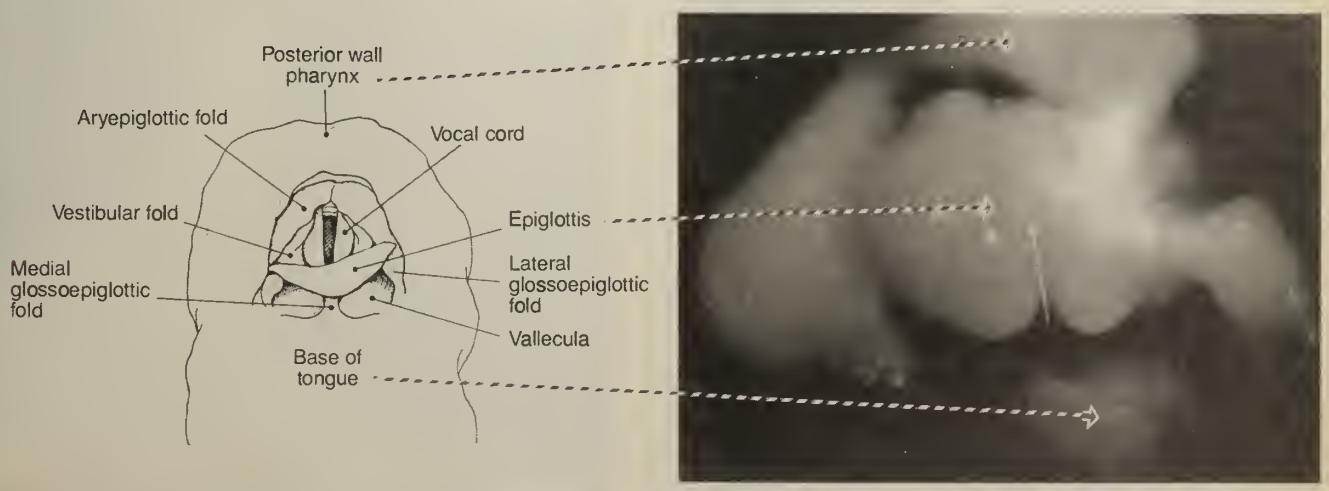

Figure 1.—The photograph taken with a flexible laryngoscope reveals an inflamed, swollen epiglottis **(arrow)** nearly obstructing the airway of patient 6. A drawing of the normal anatomy is shown for comparison.

H influenzae supports the proposal that the increased incidence of *H influenzae* epiglottitis in adults is real rather than the result of increased recognition.[17-21]

Clinical Characteristics

The age ranges noted in our series are similar to those in previous reports,[2,3,15] and equivalent sex distributions exist.[4,5,7,14] Although MayoSmith and colleagues found no significant difference in the seasonal incidence of adult epiglottitis,[2] we and others have shown that more cases occur during the winter months.[21-24]

Most investigators report sore throat and dysphagia to be the most common symptoms,[8,14,15] although fever has been reported in as many as 80% of patients.[2,3,8] Hoarseness, cervical adenopathy, neck tenderness, and pharyngitis have been noted in fewer than 30%.[3,8,15]

Unlike childhood epiglottitis, in which most children are seen with respiratory symptoms, only five of our nine adult patients had such symptoms, consistent with the findings of a previous report.[23] In Khilanani and Khatib's review of 154 cases, dyspnea occurred in 78% of patients,[8] but others have reported respiratory symptoms in 20% to 33% of patients.[3,4,14,15] The lower incidence of respiratory symptoms in adults may be related to the larger, more rigid structure of the adult larynx.[3,4,8,14,16]

The onset of symptoms tends to be more gradual in adults than in children. Most children with epiglottitis are seen within 12 hours after symptoms occur.[23] In adults, the duration of symptoms can range from 2 hours to 10 days.[8] Khilanani and Khatib found that 58% of adults presented within 24 hours,[8] and Mustoe and Strome found 64% were seen within 48 hours.[3] The mean duration of symptoms in our series was 13.9 ± 8.7 hours, and only two patients sought medical care 24 hours or longer after symptoms began.

The rapid appearance of respiratory symptoms in adults indicates a more serious illness. The assumption of an upright posture and signs of acute upper airway obstruction and drooling correlated with a high percentage of patients requiring airway intervention.[14] In patients with symptoms of less than eight hours' duration, evidence of airway compromise was found. In contrast, only 41% of patients with symptoms of longer than 12 hours' duration had airway compromise. Branefors-Helander and Jeppsson noted that all patients with symptoms of less than 24 hours' duration required intubation, but none required intubation if symptoms had been present for more than 24 hours.[13] Our most striking observation was the frequency (67%) of missed diagnoses. Schabel and co-workers and Procino found that 60% and 75% of patients in their series, respectively, were discharged with incorrect diagnoses on the initial visit.[5,6] Lower, but still substantial rates of 38%, 32%, and 23% were reported by MayoSmith and colleagues, Mustoe and Strome, and Andreassen and associates.[2-4]

Diagnosis

The first approach to diagnosis is clinical and the second is microbiologic. The clinical diagnosis of epiglottitis is based on a patient's history and either abnormal findings on laryngoscopy or a confirmatory lateral neck soft tissue roentgenogram, or both. Awareness of adult epiglottitis, however, is the most important step to diagnosis.

Figure 2.—The lateral neck radiographs depict the airway obstructed by the inflamed, swollen epiglottis (**arrow**) of patient 6 before treatment.

Figure 3.—The lateral neck radiograph done 3 weeks after successful therapy shows the normal epiglottis (**arrow**) of patient 6.

Laryngoscopy, the most sensitive and specific test, should show inflammation of the epiglottis and supraglottic structures. The laryngoscopist should be experienced and able to establish an airway rapidly should the need arise. Although laryngoscopy has been reported to precipitate laryngeal spasm in children with epiglottitis, we found no such reports in adults.[4,24,25]

Laryngeal visualization may be done either indirectly using a laryngeal mirror or directly with a fiber-optic laryngoscope or bronchoscope. Fiber-optic scopes have the added advantage of facilitating tracheal intubation by having the endotracheal tube in position over the fiberscope before the procedure is begun.[26,27]

The alternative to direct visualization is a soft tissue lateral neck roentgenogram. Its advantages are that it can be done without requiring the skills of an otolaryngologist or pulmonologist and that there is no airway manipulation so the theoretic risk of provoking airway obstruction is not present. It is, however, less sensitive and specific than direct visualization.[9] In the only study comparing roentgenography with laryngoscopy, Schumaker and colleagues used quantitative measurements on a lateral neck radiograph and achieved equal diagnostic yield.[10] An epiglottic width of less than 8 mm and an aryepiglottic fold width of less than 7 mm ruled out a diagnosis of epiglottitis in adults, whereas an epiglottic width of more than 14 mm and an aryepiglottic fold width of more than 10 mm identified all cases of epiglottitis confirmed by laryngoscopy.

We suggest that laryngoscopy be done in all patients with suspected epiglottitis. If this is not possible, then lateral neck soft tissue roentgenograms may either confirm or exclude the diagnosis if the criteria noted earlier are used. If doubt still exists, however, then laryngoscopy should be done at the earliest opportunity.

Etiology

Once a diagnosis of epiglottitis is established, therapy should begin immediately. Determining the microbial cause is important to narrow the spectrum of antibiotic therapy, to facilitate an assessment of prognosis, and for epidemiologic surveys. Throat cultures and epiglottic swabs are not useful, since organisms recovered may be normal flora.[17] Thus, confirming the causative infectious agent requires a blood culture or cultures of aspirated material from abscess sites.

Unlike childhood epiglottitis, in which more than 95% of children have a positive blood culture, most adult cases will have no growth on cultures.[28] In this series, five of nine patients (56%) had blood cultures positive for a pathogen. This is higher than the 15% to 30% yield reported in most other series.[3,14,16] In the series of Deeb and associates, 86% had positive blood cultures if symptoms were of less than eight hours' duration, but only 8% had positive cultures if symptoms were present for more than eight hours.[14] In addition, positive blood cultures are associated with the need for airway intervention and with a poor outcome.[2]

Type b *Hemophilus influenzae,* the most commonly cultured organism in both children and adults, is identified in 60% to 100% of all positive cultures.[10,12,28] In our series, four of five positive blood cultures yielded *H influenzae* type b. *Streptococcus pneumoniae* is the second most frequently cultured organism.[8,29,30] Other organisms reported include hemolytic streptococcus *(viridans, pyogenes),*[11] *Staphylococcus aureus,*[16] *Hemophilus parainfluenzae,*[31,32] *Pasteurella multocida,*[33] *Klebsiella pneumoniae,*[34] *Hemophilus paraphrophilus,*[35] and *Fusobacterium necrophorum.*[36]

The large number of culture-negative cases may represent a viral or purely inflammatory cause.[15] Alternatively, in milder cases, the duration of bacteremia may be self-limited. In cases where *H influenzae* type b is identified as the pathogen, the disease is more severe.[3,16] Two of our patients with cultures positive for *H influenzae* required intubation, and in three of the four extraepiglottic complications developed. In Mustoe and Strome's series, 70% of patients with documented *H influenzae* infections had a leukocyte count greater than 15×10^9 per liter, 80% had temperatures greater than 38.3°C (100.9°F), and 20% required a tracheostomy.[3] This was in contrast to 6% of patients without *H influenzae* who required a tracheostomy. Also, the time from the occurrence of symptoms to hospital admission was reduced compared with that in patients not infected with *H influenzae.*

Treatment

Successful treatment requires an early recognition of epiglottitis in an adult. With 67% of patients misdiagnosed on their initial presentation, many patients may not receive appropriate therapy, sometimes with fatal consequences.[37] Thus, a high level of suspicion and a low threshold for doing laryngoscopy or lateral neck roentgenograms, or both, are necessary.

All diagnosed patients should be admitted to hospital and carefully monitored, preferably in an intensive care unit. Although older series reported upper airway obstruction in as many as half of adults, with a 50% mortality, and advocated tracheostomy in all patients,[4,5,9,25,38,39] more recent series' results indicate that no more than 10% to 30% of patients will require airway intervention.[3,4,8,15] Prophylactic tracheostomy or intubation is recommended only for patients with rapidly progressive symptoms because most patients are monitored carefully and can have airway support established if necessary. Recent cases of successful airway protection in acute epiglottitis by endotracheal and nasotracheal intubation have been reported.[40,41] In McGovern and colleagues' series of 2,400 patients, endotracheal intubation carried a mortality of less than 1% versus a mortality of 3% for patients having a tracheostomy.[42,43] In a series of pediatric patients consisting of 815 children with croup and 55 with epiglottitis, the complication rate for intubation was 1.6%, whereas the mortality with tracheostomy was 3.6%.[44] Studies of smaller series of adult patients arrived at the same conclusions.[45,46] The mean duration of airway support in adult cases of epiglottitis has been reported at 40 to 60 hours.[3,47] Intubation has been shown to decrease the duration of hospital stays for epiglottitis patients as well, when compared with those having a tracheostomy.[48] Tracheostomy should be a maneuver of last resort.

In patients with a more insidious onset of symptoms or without respiratory symptoms at presentation, careful observation is recommended. Attention should be given to hydration and electrolyte and airway monitoring, as well as other associated extraepiglottic complications. There are anecdotal reports of benefits from the use of humidified oxygen, inhaled vasoconstrictors (racemic epinephrine), and steroids.[49] Although there are no controlled trials of the use of steroids in epiglottitis, it may be prudent to administer steroids parenterally for a period of 24 to 48 hours. This will

presumably decrease the inflammatory response, which may be more responsible for airway obstruction than the infection.

All patients should be started on antibiotic therapy once appropriate cultures are done. Initial treatment must be effective for resistant strains of *H influenzae* and *S pneumoniae.* Ampicillin-resistant *H influenzae* was first reported in 1974.[S0] By 1978 it represented 4.5% of cases[18] and by 1984, 14%.[S1] At our institution, 39% of *H influenzae* isolates are ampicillin-resistant. In our series two of four patients had *H influenzae* bacteremia caused by ampicillin-resistant strains.

For these reasons, we recommend the use of chloramphenicol or a β-lactamase-resistant cephalosporin such as cefuroxime[52,53] or cefotaxime as initial antibiotic therapy. Treatment failures with cefamandole in children with *H influenzae* infections have been noted.[19,S4] The choice of antibiotic can be changed once sensitivities have been determined. A total seven- to ten-day course of antibiotics should be administered.

Prognosis

In contrast to the earlier reported mortality rates approaching 50%, most recent series report mortality at 0% to 20%.[8,38,S5] In patients without respiratory symptoms on presentation, mortality is negligible.[8] Khilanani and Khatib reported that patients with respiratory symptoms had a 21.7% mortality and intubated patients a 14.3% mortality.[8] Patients requiring an elective tracheostomy had a 4.9% mortality, whereas those requiring emergency tracheostomy had a 45.5% mortality. In our series, there were no deaths.

Extraepiglottic infections have been reported, although incidence figures are lacking. The most frequent infections are pneumonia and empyema, as noted in our series. Other complications of acute epiglottitis are pericarditis,[S1] meningitis,[8] epiglottic abscess,[8] neck cellulitis,[20] and noncardiogenic pulmonary edema.[S6]

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Clinical Review

Management of Diabetes Mellitus During Surgery

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Patients with diabetes mellitus are subjected to major operations more frequently than those without diabetes. Although many of these operations are done on an elective basis, the perioperative control of blood glucose levels—ranging from 6.7 to 13.3 mmol per liter (120 to 240 mg per dl)—remains a therapeutic challenge. In planning the management, the type of diabetes, current treatment, the degree of recent control, the presence of complications, and the type of surgical procedure must all be considered. All insulin-dependent patients and many non-insulin-dependent ones need insulin therapy perioperatively. The variable stress associated with major procedures such as coronary artery bypass and kidney transplantation makes a flexible insulin regimen desirable, which can be provided using a continuous insulin (regular) infusion system and frequent bedside blood glucose monitoring. Implementing such a regimen facilitates rapid control before an operation and a quick response to blood glucose changes during the procedure and provides a convenient and predictable method of control during the postoperative period.

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The traditional management of diabetes mellitus during an operation owes little to modern advances in medical technology and a better understanding of insulin pharmacokinetics. The many different regimens used are based on dogma rather than scientific reasoning. Meticulous management and intensive care units have facilitated the apparent success of these inappropriate regimens. Fortunately, recent efforts by Alberti and co-workers[1] and Rosenstock and Raskin[2] have encouraged practitioners to use newer approaches based on logic, a better understanding of the metabolic response to surgical stress, insulin kinetics, and the pathophysiologic differences between insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus. These management protocols use a controlled insulin-glucose infusion regimen. The traditional method still widely used for controlling blood glucose levels perioperatively is to give 30% to 50% of the morning dose of an intermediate insulin suspension—isophane (NPH) or zinc (lente)—subcutaneously on the day of the procedure. This is usually combined with an intravenous infusion of a solution of dextrose 5% in water at a rate of 100 ml per hour. There are major disadvantages associated with this approach. The absorption of insulin is variable and unpredictable, and extremes in blood glucose levels frequently occur. Once administered, the insulin effect cannot be modified; thus, should the operation be delayed until the afternoon, a frequent occurrence, severe hypoglycemia can result. Postoperative care becomes labor intensive and is frequently associated with inappropriate schedules for administering regular insulin injections (subcutaneously) based on delayed laboratory blood glucose values or, worse still, urine glucose values. Therefore, regimens of continuous regular insulin infusion combined with rapid blood glucose monitoring systems used at the bedside are generally gaining acceptance for perioperative blood glucose control and are replacing the traditional approach.

Metabolic Effects of Surgery and Anesthesia

Surgical procedures cause a pronounced catabolic response (Table 1). These events are mediated by an excess production of glucagon, catecholamines, cortisol, and growth hormone and a relative insulin deficiency. The magnitude of the catabolic response depends on the type and duration of the operation and the severity of the underlying clinical disorder. The cumulative metabolic alterations result in hyperglycemia—gluconeogenesis and glycogenolysis—and mild (in non-insulin-dependent diabetes) to moderate (insulin-dependent diabetes) ketosis due to lipolysis and ketogenesis. Thus, patients will rarely have hypoglycemia unless treated with excessive insulin or they are affected by an erratic and unpredictable absorption of insulin from subcutaneous administration before the procedure. Therefore, the major risk in both types of diabetes is dehydration and electrolyte imbalance from the hyperglycemia-induced osmotic diuresis. This can be associated with considerable hemodynamic changes, poor tissue perfusion, and organ ischemia. Should this state be complicated by notable ketoacidosis, especially in patients who are insulin-dependent, severe obtundation will occur. It is important to note that serious ketosis may also develop in patients with NIDDM under severe stress.

Preoperative Evaluation

The aim of therapy should be to avoid excess morbidity or mortality compared with that in nondiabetic patients. Extremes in blood glucose levels, undue protein catabolism, and fluid and electrolyte disturbances must be prevented. These goals can be achieved by an appropriate preoperative evaluation (Table 2). A clinical assessment should be done in the office before an elective operation or, less preferably, on the day of admission to hospital. The type of diabetes should be correctly identified. Note that 20% to 30% of patients

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ABBREVIATIONS USED IN TEXT

IDDM = insulin-dependent diabetes mellitus
NIDDM = non-insulin-dependent diabetes mellitus

with type II diabetes (NIDDM) take insulin for the adequate control of blood glucose levels. They tend to have increased peripheral resistance and reduced insulin secretion perioperatively; thus, their insulin needs are frequently greater than anticipated. Patients with insulin-dependent diabetes must be given adequate insulin doses on a frequent schedule—every four to six hours—and the blood glucose cutoff for withholding an insulin dosage should not be set too high. In general, insulin either by bolus or infusion should be given unless the blood glucose levels fall to less than 5.6 mmol per liter (100 mg per dl). All too frequently, patients with IDDM slip into ketoacidosis perioperatively because of the practice of withholding insulin until blood glucose values exceed 10.0 to 13.3 mmol per liter (180 to 240 mg per dl). An insulin bolus should not be given intravenously as its biologic half-life is about 20 minutes; therefore, the effect dissipates rapidly, and ketoacidosis can develop in the subsequent four- to six-hour period.

TABLE 1.—*Endocrine and Metabolic Responses to Surgery in Diabetic Patients*

- Endocrine Response
  - Increased secretion of catecholamines, glucagon, cortisol, and growth hormone
  - Decreased secretion of insulin
  - Increased insulin resistance—non-insulin-dependent diabetes mellitus, marked
- Metabolic
  - Hyperglycemia
  - Decreased glucose use
  - Increased gluconeogenesis
  - Increased net protein catabolism
  - Variable increase in lipolysis with ketone bodies formation—insulin-dependent diabetes mellitus, marked
  - Increased metabolic rate and catabolism
- Immediate and Long-Term Effects
  - Dehydration and hemodynamic instability due to osmotic diuresis
  - Loss of lean body mass, impaired wound healing, decreased resistance to infection
  - Loss of adipose tissue
  - Deficiency of essential amino acids, vitamins, minerals, and essential fatty acids

TABLE 2.—*Preoperative Evaluation of Diabetic Patients*

- Identify diabetes type
  - Insulin-dependent diabetes mellitus
    - Absolute need for frequent insulin therapy
  - Non-insulin-dependent diabetes
    - Associated with increased insulin needs
- Determine level of preceding glycemic control
  - Self-monitoring of blood glucose levels
    - Review blood glucose records and glycosylated hemoglobin values
- Presence of diabetic complications
  - Nephropathy
    - Fluid balance, hypotension, drug dosage
  - Neuropathy (autonomic)
    - Cardiovascular response—arrhythmias, postural hypotension
    - Gastrointestinal—gastroparesis
    - Bladder dysfunction—retention
- Cardiovascular assessment
  - Coronary artery disease
  - Hypertension
  - Congestive heart failure

The history of previous glycemic control should be reviewed, and control should be improved in symptomatic and asymptomatic patients with sustained hyperglycemia, reflected by a fasting blood glucose level higher than 13.3 mmol per liter or high glycosylated hemoglobin values—more than 0.1 (10%)—or both. Improved control during the perioperative period—blood glucose values between 5.6 and 10.0 mmol per liter—should reduce the morbidity from fluid and electrolyte imbalance, decrease the risk of infection, and perhaps increase the wound-healing rate. From a practical standpoint, physicians rarely have the luxury of time to implement optimal metabolic control owing to brief preoperative hospital stays. This problem has become more pressing with the general acceptance of the system of diagnosis-related groups. Thus, diabetic patients scheduled for elective surgical treatment should be referred for outpatient evaluation whenever possible. Fortunately, the modern approach to management using insulin-glucose infusion regimens allows a rapid improvement in blood glucose levels within a few hours, facilitating a rapid preoperative preparation.

Close attention should be paid to diabetic complications such as nephropathy, autonomic neuropathy, hypertension, and coronary artery disease. Nephropathy aggravates fluid management, alters insulin pharmacokinetics (sustained effect), and necessitates a careful selection of antibiotics to avoid nephrotoxicity. Autonomic neuropathy modifies the cardiovascular response to surgery and anesthesia, producing a high arrhythmia risk. It may also magnify the risk of urinary retention and delay postoperative refeeding due to gastrointestinal disturbances. The increased prevalence of hypertension, coronary artery disease, and their complications warrants careful evaluation and management. Cardiovascular complications are the major causes of surgical mortality in diabetic patients.

Indications for Perioperative Insulin

All patients taking insulin—both insulin- and non-insulin-dependent—should receive insulin therapy during a surgical procedure (Table 3). In addition, most NIDDM patients should be given insulin during a major operation. These patients generally tend to have fasting blood glucose levels higher than 10.0 mmol per liter (180 mg per dl) and glycosylated hemoglobin values of more than 0.1. A small subset of NIDDM patients with acceptable control—fasting

TABLE 3.—*Indications for Insulin Therapy During an Operation*

- Always
  - All patients taking insulin—both insulin-dependent diabetes mellitus and non-insulin-dependent diabetes (NIDDM)
  - Patients with NIDDM treated with diet, oral hypoglycemic agents, or both but having chronic hyperglycemia (FBG > 10.0 mmol/liter and glycosylated Hb > 0.1)
- Variable
  - Patients with NIDDM treated with diet, oral hypoglycemic agents, or both, under good control
    - Current FBG ≤ 10.0 mmol/liter
    - Glycosylated Hb 0.08 to 0.1
    - Duration of operation < 2 h
    - Use of glucose solutions not planned

FBG = fasting blood glucose, Hb = hemoglobin

blood glucose of less than 10.0 mmol per liter, glycosylated hemoglobin of 0.08 to 0.1—on diet or oral hypoglycemic agents (or both) may not require this intensive approach. Such patients will need close perioperative monitoring with frequent blood glucose analyses, however. This approach is acceptable for a surgical procedure not invading a major body cavity and when the procedure is relatively simple and short—less than two hours. The latter group is covered with regular insulin given subcutaneously every two to four hours based on a blood glucose algorithm.

Estimating Insulin Requirements

There is no absolute method for correctly predicting insulin needs in patients scheduled for a surgical procedure.[3-5] Clinical experience shows, however, that most operative patients can be maintained in the blood glucose range of 6.7 to 13.3 mmol per liter with the regular insulin infusion rates set between 1.0 and 2.0 units per hour.[2,4,5] Experienced physicians can estimate with reasonable accuracy a safe insulin dosage program based on the individual patient features and the type of operation (Table 4). The initial estimates of insulin needs are based on the type of diabetes, previous therapy, the degree of glycemic control in relation to the total daily amount of insulin, and the presence of obesity, renal failure, infection, or steroid therapy. Although the extent and type of surgical treatment are important considerations in estimating insulin requirements, clinical experience with insulin infusion systems has shown remarkably similar insulin needs for most surgical procedures except for kidney transplants and coronary artery bypass grafts. Steroid therapy in patients having kidney transplants causes insulin resistance and is associated with a twofold to threefold increase in insulin needs. The combination of sympathomimetic drugs and pump priming with glucose-enriched solutions in patients undergoing coronary artery bypass graft causes dramatic—threefold to fivefold—increases in insulin needs to sustain acceptable blood glucose levels.

TABLE 4.—*Guidelines for Estimating Insulin Dose**

Type of diabetes and previous management	
All insulin-treated diabetes—>50 U/d	
Selected insulin injection dose, 36 U/d	
Base algorithm on 1.5 U/h for blood glucose level of 7.8 to 10.0 mmol/liter	
Diet, oral agents, or insulin—<50 U/d	
Selected insulin injection dose, 24 U/d	
Base algorithm on 1.0 U/h for blood level of 7.8 to 10.0 mmol/liter	
Previous control	
Acceptable	
Average FBG ≤ 7.8 mmol/liter, glycosylated Hb ≤ 0.08	
Fair control	
Average FBG ≤ 11.1 mmol/liter, glycosylated Hb ≤ 0.1	
Conditions associated with increased insulin need	
Obesity, Liver disease	Selected dose × 1.5
Severe infection, Steroid therapy	Selected dose × 2
Type of operation	
General	Selected dose
Renal transplant	Selected dose × 2
Coronary artery bypass graft	Selected dose × 3-5

FBG=fasting blood glucose, Hb=hemoglobin

*Regular insulin infusion rate—units per hour—dose per 24 hours.

Perioperative Management

Diabetic patients should be admitted the day before an elective procedure to facilitate the planning of an appropriate regimen. It is also desirable that such patients be reviewed in their physicians' office in anticipation of the operation. It is important to convert NIDDM regimens of long-acting agents (chlorpropamide and glyburide) to shorter-acting drugs (glipizide and tolbutamide) several days before hospital admission. A preoperative evaluation can be done and recommendations for management made the afternoon or evening before the operation. The insulin infusion should be started the night before for early morning procedures and for patients needing improved glycemic control. Otherwise, patients take the usual evening dose of insulin or oral hypoglycemic agent. In all patients requiring insulin, the insulin infusion must be started at least two to three hours before the operation. To successfully monitor and regulate an insulin infusion regimen, a system for the accurate measurement of blood glucose levels at the bedside must be in place. In the absence of rapid and accurate bedside blood glucose monitoring with a meter, it is not feasible to safely implement a regimen of a continuous regular insulin infusion. Furthermore, the anesthesiologist must do a blood glucose analysis every hour during the operation and adjust the insulin infusion accordingly.

Day of Operation

A major operation is defined as any procedure requiring a general anesthetic. Thus, procedures considered simple but subsequently unexpectedly complicated will be appropriately managed.

There are two basic regimens for administering insulin and glucose.[1,2,6] The preferred method uses a separate infusion of insulin and glucose by dedicated pumps to allow independent adjustments of each infusion rate (Table 5). This approach provides flexibility and can be rapidly adjusted depending on the hourly variation in blood glucose values. The alternate method is to combine insulin and the maintenance fluids—preferably 5% dextrose in a solution of ½N saline—at a pre-estimated individualized concentration (Table 6). This method lacks the flexibility frequently needed for a complicated operation such as a kidney transplant and coronary artery bypass grafts. It is an acceptable method for many elective procedures, however, when infusion pumps are not available and when frequent variations in insulin needs are not anticipated.

The success of either of the insulin-glucose infusion regimens is dependent on hourly, accurate measurements of blood glucose levels. A bedside blood glucose monitoring system must be in place to guarantee optimal care during the perioperative period. Such a program consists of personnel (nurse or laboratory technician) certified in bedside blood glucose monitoring with a meter, skilled in the use of insulin-glucose infusion systems, and supported by appropriate quality control. The same principles apply during the procedure. Thus, the anesthesiologist is a critical member of this team approach and must be involved in the preoperative planning.

The blood glucose monitoring and adjustments continue during the operation and in the recovery room. Close collaboration is needed among all parties—attending physician, anesthesiologist, surgeon, and nurses—of a diabetic care team. The infusion is continued until the patient is tolerating

oral feeding. Excellent glycemic control can be achieved for brief (12 hours) to prolonged (more than 72 hours) postoperative periods.

The example provided in Table 5 is an algorithm based on hourly blood glucose analyses that will maintain blood glucose control during most surgical procedures. The regimen has the flexibility to meet individual patient needs. Physicians should be careful when temporarily stopping the infusion for a blood glucose level of less than 4.4 mmol per liter (80 mg per dl). Insulin given intravenously has a plasma half-life of 5 minutes and a biologic effect for about 20 minutes.[1] Thus, even a brief period of insulin deficiency, especially in a patient with insulin-dependent diabetes, may allow a rapid deterioration in metabolic control. Episodes of blood glucose values of 4.4 mmol per liter or less are managed as indicated in Table 5.

The less flexible but extremely safe and convenient combined insulin and glucose regimen is outlined in Table 6. Once more, the guidelines provided are examples and may need further individual modification. Two levels of therapy are provided, depending on the previous mode of therapy. The fasting blood glucose level before therapy is used to further modify the insulin dose to avoid the need for a subsequent change in the intravenous preparation. This approach will maintain perioperative blood glucose levels in a safe range—6.7 to 13.3 mmol per liter—for 80% of operations,[1] and hypoglycemia is rare. The method lacks the flexibility of the separate insulin-glucose infusion regimens, however, which may be desirable in many major operations. Careful monitoring of potassium levels is needed during insulin and glucose infusions. Thus, maintenance fluids should contain at least 20 mEq per liter of potassium for patients with normal serum potassium values and modified accordingly depending on perioperative variation.

TABLE 5.—*Algorithm Guidelines for Perioperative Diabetes Management of Separate Insulin and Glucose Infusions*

Insulin
- Regular, 25 U, in 250 ml N saline (1 U per 10 ml)

Infuse insulin intravenously from an infusion pump; flush 50 ml through line before connecting to patient; piggyback this line to the perioperative maintenance fluids infusion line

Monitor blood glucose levels hourly during operation and every 2-4 h before and after operation once stable

Perioperative maintenance fluids must contain dextrose (5%)

Do the initial blood glucose measurement "stat" in the clinical laboratory

Blood Glucose mmol/liter	Blood Glucose (mg/dl)	Insulin U/h	Insulin ml/h	Fluids, ml/h
≤ 4.4	(≤80)	0.0	0.0	125
4.5- 5.5	(81-100)	0.5	5.0	125
5.6- 7.8	(101-140)	1.0	10.0	125
7.9-10.0	(141-180)	1.5	15.0	125
10.1-12.2	(181-220)	2.0	20.0	125
12.3-14.4	(221-260)	2.5	25.0	100
14.5-16.6	(261-300)	3.0	30.0	100
16.7-18.9	(301-340)	4.0	40.0	100
>18.9	(>341)	5.0	50.0	100

Blood glucose ≤4.4 mmol/liter, bolus with 50% dextrose in water (25 ml); once blood glucose >4.4 mmol/liter, restart insulin infusion and recheck in 30 min

Decreased insulin needs
- Patients treated with diet, oral agents, or <50 U insulin per day

Increased insulin needs
- Sepsis, steroid therapy (renal transplant), coronary artery bypass

If high-dose insulin is anticipated, a more concentrated insulin solution should be prepared to avoid excessive fluid intake

Postoperative Care

During the immediate postoperative period, the insulin-glucose infusion is continued until the patient can tolerate an adequate dietary intake. Subsequent to the infusion regimen, patients are managed on a schedule of multiple insulin injections (Table 7). The most convenient is a schedule of premeal boluses with regular insulin injections adjusted on a premeal blood glucose sliding scale and a small dose (10 to 20 units)

TABLE 6.—*Algorithm Guidelines for Perioperative Diabetes Management Using Combined Insulin and Glucose Infusions*

Diabetes treated with diet, oral agent, or insulin (<50 U/d)
- Add 10 U regular insulin to 1,000 ml of 5% dextrose
- Infuse at 100 ml/h (rate, 1.0 U/h)—FBG, 6.7 to 13.3 mmol/liter (120-240 mg/dl)
- If initial blood glucose >13.3 mmol/liter, add 15 U regular insulin to 1,000 ml (1.5 U/h)
- If initial blood glucose <6.7 mmol/liter, add 5 U regular insulin to 1,000 ml (0.5 U/h)
- Check blood glucose level hourly

Insulin-treated diabetes (>50 U/d)
- Add 15 U regular insulin to 1,000 ml of 5% dextrose
- Infuse at 100 ml/h (rate 1.5 U/h)—FBG, 6.7 to 13.3 mmol/liter (120-240 mg/dl)
- If initial blood glucose >13.3 mmol/liter, add 20 U regular insulin to 1,000 ml (2.0 U/h)
- If initial blood glucose <6.7 mmol/liter, add 10 U regular insulin to 1,000 ml (1.0 U/h)
- Check blood glucose level hourly

Blood glucose ≤4.4 mmol/liter, stop infusion bolus with 50% dextrose in water (25 ml), once blood glucose >4.4 mmol/liter, restart infusion and recheck blood glucose level in 30 min

Increased insulin needs
- Sepsis, steroid therapy (renal transplant), coronary artery bypass graft

FBG=fasting blood glucose

TABLE 7.—*Guidelines for Postoperative Diabetes Management*

Once patient tolerates diet, stop insulin-glucose infusion after first subcutaneous insulin injection

Measure blood glucose level before meals and at 10 PM (3 AM when indicated)

Begin 3 meals and before-bedtime snack (25 cal/kg)

Prescribe preprandial insulin injection, given subcutaneously, according to the following algorithm

Blood Glucose mmol/liter	Blood Glucose (mg/dl)	Breakfast (U)	Lunch (U)	Dinner (U)
≤4.4	(≤80)	4	2	3
4.5- 5.5	(81-100)	5	3	4
5.6- 7.8	(101-140)	6	4	5
7.9-10.0	(141-180)	7	5	6
10.1-12.2	(181-220)	8	6	7
12.3-14.4	(221-260)	10	7	8
14.5-16.6	(261-300)	12	8	10
>16.6	(>300)	14	10	12

Add overnight coverage with isophane insulin suspension (NPH), 10-20 U, at 10 PM

The variability in food intake will necessitate tailoring of these doses for each patient

of intermediate insulin suspension, isophane or zinc, at bedtime to cover overnight. Frequently an additional blood glucose measurement is required at 3 AM to determine the glucose nadir. This approach is initially used for most insulin-treated patients. When a patient becomes stable with regard to glycemic control and postoperative complications, the standard insulin regimen is restarted. Some patients, however, may revert to their usual insulin regimen once food tolerance is established. Patients previously managed with diet and oral hypoglycemic agents may also frequently need the multiple insulin regimen for one to three days for glycemic control before reverting to their former therapy.

Emergency Surgical Care

Diabetic patients require close attention when admitted for an emergency operation. The stress of an acute event frequently precipitates a deterioration in glycemic control, which may progress to diabetic ketoacidosis. Thus, the first priority is to assess glucose control, level of hydration, and acid-base status. Preoperative management will require an aggressive approach to correct fluid and electrolyte imbalances, reverse acid-base disorders, and optimize blood glucose levels. In the presence of ketoacidosis, the operation should be delayed for four to six hours when possible while the patient is given standard therapy. Separate insulin and fluids infusion systems are excellent for such intercurrent management. The insulin dose (rate per hour) and fluid needs should be tailored to each patient according to the severity of the metabolic decompensation and the patient response. The management of ketoacidosis involves higher insulin infusion rates—0.1 units per kg body weight per hour—than outlined in Table 5. The infusion is generally preceded by an injection of regular insulin (10 units). Adjustments are then made according to hourly blood glucose levels. Once blood glucose values return to 13.3 mmol per liter, 5% dextrose should be included in the rehydration fluids. Adequate potassium replacement is critical, as is close monitoring of fluid balance, acid-base status, electrolytes, and renal function. Once a patient's condition is stable—four to six hours—the operation can be done safely. Furthermore, reversal of the acute stressful condition will require lower insulin infusion rates for a given blood glucose level.

TABLE 8.—*Guidelines for Diabetes Control for Minor Surgical and Diagnostic Procedures*

Insulin-treated patients
- NPO day of operation
  - Hold morning isophane insulin or insulin zinc suspension
  - Check FBG and give insulin injection subcutaneously (SC)
  - Give regular insulin every 4-6 h by the blood glucose algorithm

Blood Glucose, mmol/liter	*(mg/dl)*	*Insulin, Regular, SC, U*
≤ 4.4	(≤80)	0
4.5- 5.5	(81-100)	2
5.6- 7.8	(101-140)	3
7.9-10.0	(141-180)	4
10.1-12.2	(181-220)	5
12.3-14.4	(221-260)	6
14.5-16.6	(261-300)	8
>16.6	(>300)	10

  - Give evening insulin dose according to dietary tolerance
- Breakfast allowed
  - Normal morning insulin dose check—blood glucose every 2-4 h
  - Supplement with insulin injection—blood glucose >12.2 mmol/liter: 5 U
  - Avoid hypoglycemia

Patients treated with oral hypoglycemic agent (OHA)
- NPO day of operation
  - Hold morning OHA
  - Check blood glucose before and after operation
  - Give evening OHA
    - Insulin rarely needed; if necessary, use human regular insulin SC injection

Blood Glucose, mmol/liter	*(mg/dl)*	*Insulin, Regular, SC, U*
≤ 9.9	(≤180)	0
10.0-12.2	(181-220)	5
12.3-14.4	(221-260)	6
14.5-16.6	(261-300)	8
>16.6	(>300)	10

- Breakfast allowed
  - Normal morning OHA
  - Check blood glucose before and after operation
  - Give evening OHA

FBG=fasting blood glucose, NPO=nothing by mouth *(nulla per os)*

Minor Surgical Procedures

The most frequently requested diabetes consultation is for guidance during minor operations. In the absence of a need for general anesthesia, breakfast may or may not be withheld. In addition, many patients undergoing invasive diagnostic procedures that are frequently protracted will be on a regimen of "nothing by mouth." Thus, food intake must always be considered in a patient's evaluation. Furthermore, the management plan must consider the type of diabetes, the mode of therapy, and the availability of bedside blood glucose monitoring. Table 8 outlines management guidelines for diabetes control during minor operative procedures. Diabetic patients taking insulin—whether they are insulin-dependent or non-insulin-dependent—are treated by the same method. The morning insulin suspension is withheld for patients who are receiving nothing by mouth and insulin cover provided on a subcutaneous insulin injection sliding scale that is adjusted for blood glucose values. If breakfast is allowed, the previously described insulin regimen is prescribed. Knowledge of a patient's blood glucose levels at frequent intervals will facilitate responses to avoid hyperglycemia or hypoglycemia. Patients on diet or oral hypoglycemic agents rarely need supplemental insulin injections for minor surgical procedures.

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Medical Progress

Cardiac Abnormalities in Liver Cirrhosis

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Cirrhosis is associated with several circulatory abnormalities. A hyperkinetic circulation characterized by increased cardiac output and decreased arterial pressure and peripheral resistance is typical. Despite this hyperkinetic circulation, some patients with alcoholic cirrhosis have subclinical cardiomyopathy with evidence of abnormal ventricular function unmasked by physiologic or pharmacologic stress. Florid congestive alcoholic cardiomyopathy develops in a small percentage, but the concurrent presence of cirrhosis seems to retard the occurrence of overt heart failure. Even nonalcoholic cirrhosis may be associated with latent cardiomyopathy, although overt heart failure is not observed. Tense ascites is associated with some cardiac compromise, and removing or mobilizing ascitic fluid by paracentesis or peritoneovenous shunting results in short-term increases in cardiac output. Cirrhosis also appears to be associated with a decreased risk of major coronary atherosclerosis and an increased risk of bacterial endocarditis. Small hemodynamically insignificant pericardial effusions may be seen in ascitic patients. The release of atrial natriuretic peptide appears to be unimpaired in cirrhosis, although the kidney may be hyporesponsive to its natriuretic effects.

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Let my liver rather heat with wine,
than my heart cool with mortifying groans.
WILLIAM SHAKESPEARE
The Merchant of Venice

Shakespeare's merchant, Antonio, may have been a shrewd businessman, but his medical knowledge was not sage, as he apparently failed to recognize that overheating his liver might "cool" his heart. During the past four decades, with the development of sophisticated techniques for measuring cardiac performance, much has been discovered about the cardiovascular abnormalities associated with liver disease. In fact, it is now clear that many facets of the circulation are deranged in patients with chronic liver disease: abnormal regional hemodynamics have been described in the splanchnic, hepatic, renal, and pulmonary vascular beds. Readers are referred to recent reviews of the alterations in these regional circulations.[1-5] In this review I will concentrate on the cardiac abnormalities found in chronic liver disease.

Hyperkinetic Circulation

Patients with liver disease have a hyperkinetic circulation: the cardiac output is increased, and arterial blood pressure and total peripheral resistance are decreased. The elevated cardiac output was first documented by Kowalski and Abelmann in 1953[6] and subsequently confirmed by numerous studies.[7-11] The increased output is due to augmentation of both stroke volume and heart rate. Not all patients show this abnormality, however; in the different series, 30% to 70% of cirrhotic patients have increased cardiac output. Nevertheless, the mean cardiac output of any group of patients with cirrhosis is invariably higher than that of a matched control group. Indeed, an intriguing observation is that the degree of circulatory hyperkinesis seems to be correlated with the degree of hepatocellular insufficiency—that is, the worse the liver function, the higher the cardiac output.[12-15] In one study, patients with Child-Pugh class A (best liver function), B, and C (poorest function) liver disease had mean cardiac indexes of 3.5, 4.0, and 4.7 liters per minute per m^2, respectively.[14]

The situation becomes yet more complicated by the observation that hepatocellular dysfunction is not even necessary for the development of a hyperkinetic circulation. Patients with portal hypertension due to portal vein obstruction, who have essentially normal liver function, will also have a hyperkinetic circulation.[16] Cirrhotic dogs without intrahepatic hypertension do not have a hyperkinetic circulation.[17] It thus appears that portal hypertension, rather than hepatic dysfunction, is prerequisite for the development of circulatory hyperkinesis. Studies in animals also support this conclusion: a hyperkinetic circulation develops in conscious rats[18] and rabbits[19] with prehepatic portal hypertension, as well as cirrhotic rats[20] and dogs.[21]

The etiology of this circulatory hyperkinesis is still obscure. It has been suggested that the development of portosystemic collateral vessels, an invariable consequence of portal hypertension, allows gut-derived vasoactive substances to bypass hepatic inactivation. These substances might then cause either direct cardiostimulation or peripheral vasodilatation. Vasoactive substances that could con-

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This work is dedicated to my father, Jae Rak Lee, MD, on the occasion of his Han-kap (60th birthday).
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TABLE 1.—*Abnormal Cardiovascular Responses to Physiologic Stimuli in Patients With Cirrhosis*

Stimulus	*Expected or Normal Response*	*Observed Response*	*Source*
Exercise	↑ Cardiac output; no change in pulmonary wedge pressure	Blunted inotropic response	Gould et al, 1969[41]; Kelbaek et al, 1984[42]
		↑ Pulmonary wedge pressure	Gould et al, 1969[41]
Eating	↑ Splanchnic blood flow; no change in cardiac output	Earlier onset of splanchnic hyperemia; decreased cardiac output	Lee et al, 1988[43]
Upright tilting	Tachycardia; stable blood pressure	Blunted tachycardiac response	Lunzer et al, 1975[44]; Bernardi et al, 1983[45]
		Fluctuations in blood pressure	Lunzer et al, 1975[44]
Valsalva maneuver	Bradycardia	Blunted bradycardiac response	Lunzer et al, 1973[46]
Deep respirations	Physiologic sinus arrhythmia	No change in heart rate	Decaux et al, 1986[47]
Cold stimulation	Bradycardia	Blunted bradycardiac response	Lunzer et al, 1975[44]

↑=increased

TABLE 2.—*Abnormal Cardiovascular Responses to Drug Infusions in Patients With Cirrhosis*

Drug	*Expected or Normal Response*	*Observed Response*	*Source*
Angiotensin II	↑ Stroke work index (SWI); no change in pulmonary wedge pressure	Blunted ↑ SWI; ↑ pulmonary wedge pressure	Limas et al, 1974[48]
Tyramine	↑ Blood pressure	Blunted pressor response	Mashford et al, 1962[9]
Isoproterenol hydrochloride	Tachycardia	Blunted tachycardiac response	Lenz et al, 1985[49]; Ramond et al, 1986[50]
Dobutamine	↑ Stroke volume	No change in stroke volume	Mikulic et al, 1983[51]
Ouabain	↑ Ventricular contractility	No change in contractility	Limas et al, 1974[48]

↑=increased

ceivably play this role include glucagon,[22,23] histamine,[24] serotonin,[25,26] and vasoactive intestinal polypeptide.[27] Added support for this hypothesis comes from the observation that creating a portosystemic shunt, such as a portocaval shunt, even in animals with normal livers, results in an increased cardiac output and decreased peripheral resistance.[28,29] In patients with cirrhosis, creating similar portocaval shunts increases the cardiac output even further.[30,31] Construction of a peripheral arteriovenous anastomosis will increase the cardiac output,[32] but if these anastomoses are created in the splanchnic bed, thus interposing the liver in the circuit, the cardiac output remains unchanged.[33] An alternative explanation, however, may be purely hemodynamic—that is, that surgically or naturally occurring portosystemic anastomoses allow blood from the splanchnic venous bed to bypass the liver resister and shunt directly into the central compartment.

The cardiac output can be increased by an augmentation of the plasma volume, and this is known to occur in cirrhosis.[7,8,34,35] A substantial portion of the volume appears to be sequestered in the capacitance vessels, however, and the circulation behaves as if there were a decrease in the actual circulating volume. This phenomenon has been termed the decreased "effective blood volume."[36(p288)] Unfortunately, because this effective volume cannot be quantified in any way, it is difficult to substantiate or refute this hypothesis. Cardiac output is not correlated with plasma volume expansion in cirrhotic patients,[8,11,37] and currently the weight of opinion is against the view that volume expansion is a major contributory factor in the pathogenesis of the hyperkinetic circulation.

Hypoxemia can also occur in patients with cirrhosis. Most patients, however, have arterial oxygen pressures in the normal range and therefore no sign of overt tissue hypoxia. Nevertheless, some of these patients show a subtle sign of tissue hypoxia: an abnormal oxygen supply dependency.[38] In other words, whole body oxygen uptake appears to be directly linked to oxygen transport. Normally, above a critical threshold value increasing oxygen availability by increasing oxygen transport does not result in increased oxygen uptake. In states of tissue hypoxia, however, such as the adult respiratory distress syndrome, increasing oxygen delivery to tissues results in proportional increases in oxygen consumption, suggesting that the tissues are actually in an oxygen-deficient state.[39] Based on these observations, it has been suggested that a state of subclinical or latent tissue hypoxia also occurs in cirrhosis.[38] Furthermore, it has been opined that in both acute[40] and chronic liver failure,[38] cardiac output increases as a homeostatic compensatory mechanism to increase tissue oxygen transport and thereby relieve the latent tissue hypoxia.

It is possible that many of the aforementioned factors are involved in the pathogenesis of the hyperkinetic circulation. Because cirrhosis is the end result of diverse insults to the liver, it is possible that the pathogenesis of hyperkinesis is indeed multifactorial. Further research is needed to elucidate these mechanisms.

Cirrhotic Cardiomyopathy

Paradoxically, despite the existence of a hyperkinetic circulation, an uncertain but probably substantial percentage of patients with cirrhosis have overt or subtle evidence of impaired ventricular contractile function (Tables 1 and 2).[41-51] The issues are complicated by the fact that in western countries, alcohol use represents one of the commonest causes of both cirrhosis and cardiomyopathy. Thus, separating the effects of alcohol and the possible effects of liver disease on ventricular function is sometimes difficult. Despite the tendency of patients with cirrhosis, particularly alcoholic patients, to be malnourished, true beriberi cardiomyopathy appears to be relatively rare, as the great majority of cirrhotic patients with cardiomyopathy fail to respond to thiamine supplementation.[52,53]

Over the past two decades, many studies have investigated the problem of cardiac dysfunction seen in alcoholic patients and those with alcoholic cirrhosis.[41,42,48,53-58] It ap-

pears that this dysfunction encompasses a spectrum ranging from asymptomatic patients with a hyperkinetic circulation and evidence of abnormal ventricular contractility only with stress, to patients with end-stage, dilated, low-output cardiomyopathy. In the former group, the peripheral vasodilatation and reduced systemic vascular resistance can affect cardiac function. This decrease in afterload may not only mask signs of overt ventricular failure but probably protects the heart from florid decompensation until late in the disease course. Many studies have shown normal or hyperdynamic resting ventricular contractility, with subsequent abnormal responses that only manifest themselves if the ventricle is physiologically or pharmacologically stressed. Gould and coworkers catheterized patients with chronic alcoholic liver disease and found resting cardiac outputs to be increased with normal left ventricular filling pressures.[41] On exercise, however, all patients had increased left ventricular end-diastolic and pulmonary artery pressures but the stroke index fell or remained the same; this pattern represents a clearly abnormal ventricular response. Limas and colleagues studied patients with alcoholic cirrhosis and no clinical evidence of heart disease.[48] They found, in the resting state, a high cardiac output, low peripheral vascular resistance (mean, 825 dynes per second per cm^{-5}), and normal pulmonary capillary wedge pressure. Infusing the vasoconstrictor angiotensin in doses sufficient to "normalize" the peripheral vascular resistance to 1,140 dynes per second per cm^{-5} doubled the pulmonary wedge pressure, but the cardiac output remained unchanged. Kelbaek and associates studied asymptomatic patients with alcoholic cirrhosis.[42] In the resting state, echocardiographic systolic time intervals and radionuclide ventricular ejection fractions were not different from those of age-matched controls. With exercise, the left ventricular ejection fraction increased only 6% in cirrhotic patients versus 14% in controls, a significant difference. In a study of patients with predominantly alcoholic cirrhosis, even a physiologic stimulus of a liquid meal produced small but substantial decreases in cardiac output.[43]

Because alcoholic cirrhosis and cardiomyopathy share a common cause, the two conditions might frequently be expected to coexist in the same patient. Studies, however, support the clinical impression that the combination of the two is relatively rare.[11,52-54] Perhaps this represents underdiagnosis—that is, there may be some substance to the cardiologists' opinion that hepatologists cannot hear gallop rhythms and the hepatologists' suspicion that cardiologists rarely examine anything below the diaphragm. Two other factors are likely much more important in explaining this apparent rarity of concurrence. One is Berkson's bias. In 1947 Berkson's statistical analyses suggested that any two lethal diseases will show a negative association at autopsy.[59] Subsequent testing of his hypothesis has confirmed this artifactual negative association for diseases such as cirrhosis and hepatic metastases as well as brain tumor and myocardial infarction.[60,61] The second and probably most important factor is the previously mentioned protective effect of low peripheral resistance in unloading the ventricles. A patient will probably die of cirrhosis before overt congestive cardiomyopathy can develop.

In patients with nonalcoholic cirrhosis, florid low-output congestive cardiomyopathy has not been described in the absence of hypertension, ischemia, or some other known cause of heart failure. Nevertheless, there are reasons to believe that cirrhosis per se may be associated with subtle evidence of abnormal contractile function. First, on theoretic grounds, hyperkinetic circulatory changes may induce a high-output cardiac failure resembling a chronic volume overload of the heart.[52,53] Second, cirrhosis of any cause is associated with high serum catecholamine levels,[62] and long-term cardiac exposure to elevated catecholamines is known to result in cardiomyopathy.[63] Third, necropsy series of patients with predominantly alcoholic or predominantly nonalcoholic cirrhosis show similar cardiac pathologic findings: mild diffuse fibrosis, subendocardial edema, nuclear and cytoplasmic vacuolation, and ventricular dilatation and hypertrophy.[64,65] Fourth, there is good evidence that jaundice itself, regardless of the cause, may exert some cardiodepressant effects.[66] Finally, some animal models of nonalcoholic liver disease also show abnormal cardiac responsiveness. Volume infusion in rats with carbon tetrachloride-induced cirrhosis causes acute ventricular failure with a 50% decrease in cardiac output.[67] Rats with prehepatic portal hypertension[68] as well as biliary cirrhosis[69] display impaired chronotropic responses to the β-adrenergic agonist isoproterenol. Ventricles from the latter group were recently found to have diminished β-adrenergic-receptor density, thus indicating that the catecholamine hyposensitivity was associated with receptor downregulation.[69] Similar β-receptor downregulation has been found in ventricles from failing human hearts.[70]

Myocardial membrane receptor studies of human cirrhosis have not been done, presumably owing to the difficulty in obtaining cardiac tissue in vivo. Lymphocyte β_2-receptors, however, correlate well with the predominantly β_1-receptors in ventricles,[71] and in a subgroup of patients with decompensated cirrhosis, Gerbes and colleagues found reduced lymphocyte β-receptor density.[72] Clearly, further research in receptor and cellular pathophysiology in cirrhotic cardiomyopathy is needed.

What are the treatment options in patients with cardiac decompensation? In alcoholic patients, abstinence could be expected to improve or at least slow the rate of deterioration of hepatic and cardiac function.[52,53,73,74] Prolonged bed rest was helpful in one study of alcoholic cardiomyopathy, although this may have been due to the effects of abstinence.[75] As for active treatment in all types of cirrhotic patients, those with normal resting cardiac function should not need drug therapy. Those with more overt heart failure should have careful drug treatment to change cardiac loading conditions.[76,77] Studies in cirrhotic patients with latent ventricular dysfunction[48] and in jaundiced dogs[78] showed that cardiac glycosides were completely ineffective in improving ventricular contractility, so at present, any possible role for digitalis compounds remains speculative.

Ascites

Ascites is a common complication of hepatic sinusoidal portal hypertension. To discuss all the hemodynamic derangements associated with ascites is not the intent of this review, but certain aspects of ascitic fluid accumulation and resolution are worth noting, as they bear directly on cardiac function. Massive ascites can affect the measurement of cardiac performance indexes directly and also artifactually. The latter refers to a misleading calculation for the cardiac index, which is obtained by dividing the cardiac output by the body surface area. Because the surface area is usually derived from tables or nomograms based on height and weight, it is

evident that the presence of as much as 20 to 25 kg of ascitic fluid will lead to an underestimation of the cardiac index unless an estimated "dry" body weight is used. Tense ascites may directly impair the cardiac performance by a hydrostatic pressure on the diaphragm, with consequent increased intrathoracic and intrapleural pressures and a decrease in the cardiac transmural filling pressure. In addition, many patients have small diaphragmatic lymphatic channels, which allow ascitic fluid to track up into the pleural cavity and thereby impair cardiac function by the same mechanism. If these hypotheses are correct, then withdrawing ascitic fluid should result in an increased cardiac output. Indeed, most studies on the hemodynamic effects of paracentesis have found significant increments in cardiac output following the procedure.[79-81] In other studies, no changes in the cardiac output were found,[82,83] but this may be related to differences in the amount of fluid removed, the timing of the cardiac output measurement after paracentesis, and whether or not albumin was concurrently infused. It appears that ascitic fluid quickly starts reaccumulating, and if peripheral interstitial edema is absent, the reaccumulation will be at the expense of the intravascular fluid compartment. Thus, remeasuring the cardiac output several hours after a paracentesis may be too late to detect the initial hemodynamic changes.

Ascitic fluid can also be removed from the peritoneal cavity by a peritoneovenous shunt such as a LeVeen or Denver shunt. In this case, however, the fluid is shunted directly into the central veins. Thus, the cardiac output would be expected to rise in the immediate postoperative period because of a decrease in intra-abdominal pressure and a direct increase in venous return. Blendis and colleagues have shown this to be the case: the cardiac output rose from a mean of 7 liters per minute to 10 liters per minute in such patients.[84] If the cardiac reserve was borderline, such a volume challenge might have precipitated pulmonary congestion, but pulmonary wedge pressures did not change, indicating a normal cardiac response. Two weeks to two months after shunt insertion, cardiac output values had returned to the preoperative levels,[84,85] suggesting a "resetting" of cardiac output controls to adjust to the long-term hemodynamic changes of peritoneovenous shunting.

Coronary Atherosclerosis

There is a pervasive view among physicians that cirrhosis, particularly alcoholic in origin, protects against the development of ischemic heart disease. The evidence in favor of this notion derives from several sources. Autopsy studies of large numbers of cirrhotic patients reveal a lower prevalence of both significant coronary atherosclerosis and myocardial infarctions.[86-88] For example, one study showed that 3.3% of cirrhotic patients died of myocardial infarction whereas the corresponding figure in patients without cirrhosis was 11.4%.[88] Other evidence comes from coronary arteriography, which in persons with chronic alcoholism usually shows no major atherosclerotic lesions.[89] Finally, epidemiologic data indicate that a modest daily alcohol intake—about two drinks per day—is associated with a decrease in the incidence of coronary ischemic events.[90,91]

Although Berkson's bias could again partly account for these observations, it is unlikely to be the sole factor. The most plausible explanation is that cirrhosis, especially alcoholic cirrhosis, modifies two of the major risk factors for coronary atherosclerosis. First, the pathophysiologic effects of alcoholism and chronic liver disease on lipids are complex. The previously mentioned protective effect of modest alcohol intake on atherosclerosis may be related to increases in high-density-lipoprotein cholesterol levels,[92] as it seems that this form of cholesterol somehow hinders arterial atherogenesis. With increasing alcohol intake and the consequent development of chronic liver disease, however, the lipoprotein profiles are further modified in patterns that are not yet fully determined. An example of the complexity of the situation is the lipid pattern of patients with primary biliary cirrhosis. Despite the high lipid levels leading to xanthomas, ischemic vascular events are distinctly rare. The likely explanation lies in the observation that in the early to middle stages of the disease, very-low-density-lipoprotein levels are normal while those of high-density lipoprotein are high. Only in the advanced stages do very-low-density-lipoprotein levels increase while the high-density-lipoprotein levels fall.[93]

The second factor may be that cirrhosis is associated with a fall in the arterial pressure. While it is now clear that alcohol abuse per se aggravates arterial hypertension, once alcoholism has led to the development of cirrhosis, the hypotensive effect of the liver disease outweighs the hypertensive effect of alcohol.[94,95] Furthermore, established cirrhosis of any cause is associated with peripheral vasodilatation and reduced arterial pressure. Such hypotension thus removes a major risk factor for coronary atherosclerosis.

Endocardial and Pericardial Disease

Because the liver acts as a "filter" for the gut circulation, a diseased liver may have difficulty in properly removing bacteria from the portal vein. This impaired ability to process gut bacteria, with a consequent "spillover" into the systemic circulation, is thought to be a major reason for the polyclonal gammopathy characteristically seen in chronic liver disease.[96] In addition, liver failure is associated with immune system defects in chemotaxis, opsonization, and phagocytosis.[97,98] A cirrhotic patient would therefore theoretically be at risk for bacterial endocarditis. The only study to address this issue is that of Snyder and co-workers.[6] On reviewing the records of 41,151 hospital admissions, they found the incidence of endocarditis in patients with cirrhosis to be 0.34% versus 0.1% in noncirrhotic patients. Cirrhotic patients, therefore, are apparently susceptible to the development of endocarditis, although the overall risk is still fairly low.

Although it is well known that constrictive pericarditis can cause cardiac cirrhosis, the converse, cirrhosis causing pericardial disease, is practically unstudied. In rare cases, fibrinous pericarditis in the acute renal failure of the hepatorenal syndrome has occurred.[99,100] In an autopsy review of 220 cases of alcoholic cirrhosis, fibrinous pericarditis was found in 18 patients.[101] Although 15 of the 18 patients had overt azotemia, 3 had evidence of only mild renal impairment. Interestingly, no pericarditis was found in 71 patients with nonalcoholic hepatitis or cirrhosis. Because all 28 patients described in the three series have been alcoholic, it has been suggested that a synergistic effect of alcoholism and mild or overt uremia may somehow predispose to the development of fibrinous pericarditis.

A recent echocardiographic study of 27 patients with alcoholic cirrhosis documented small pericardial effusions in 63%, all associated with gross ascites.[102] The pericardial

effusions regressed with effective treatment and resolution of the ascites. No patient had evidence of cardiac tamponade or notable hemodynamic impairment. Because small pericardial effusions can be seen in other edematous states such as the nephrotic syndrome, these observations are not surprising.

Cardiac Endocrine Function

The only hormone known to be secreted by the heart is atrial natriuretic peptide, or atriopeptin.[103] Human atriopeptin is a 28-amino acid peptide stored in and released from atrial granules, with natriuretic and vasoactive properties. Currently much interest is being focused on this peptide in the sodium and water retention of cirrhosis. A discussion of this issue is inappropriate for this review, and readers are referred to recent reviews.[103,104] Suffice it to say that in patients with cirrhosis, serum levels are elevated,[104-106] the kidney appears to be desensitized to its effects,[104,105] and the atrial release of this hormone appears to be unimpaired.[106]

Conclusions

The heart and liver are closely interrelated, with disease processes in one affecting the function of the other. Although the systemic and regional circulations become hyperkinetic in cirrhosis of the liver, the pathogenetic mechanism for this is still unclear. Despite basal hyperkinesis, some patients have evidence of overt or latent cardiomyopathy. Almost all the investigation in these areas up till now has been merely descriptive or phenomenologic. With the recent emergence of advanced in vitro techniques such as membrane receptor assays and methods to characterize postreceptor membrane function, further insights into the biochemical and cellular pathophysiology of cardiac dysfunction in cirrhosis should be forthcoming. In the meantime, many questions remain. Is nonalcoholic cirrhosis in humans associated with cardiomyopathy? Are cirrhotic patients truly protected from vascular atherosclerosis, and, if so, by what mechanisms?

Another important issue is that of orthotopic liver transplantation. Many chronic liver diseases with a formerly bleak prognosis, such as primary biliary cirrhosis, can be treated with transplantation. The disappearance or regression of signs such as ascites, bounding peripheral pulses, and resting tachycardia in a stable allograft recipient suggests that many of the cardiovascular complications of cirrhosis are wholly or partially reversible. Research in this area may help elucidate the fundamental pathophysiology of circulatory disturbances in liver disease.

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Medical Staff Conference

Iatrogenic Illness

Discussant
LAWRENCE M. TIERNEY, Jr, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Iatrogenic illness is an uncomfortable subject that is rarely the focus of scientific study. In his remarks today, Larry Tierney, MD, will bring to bear on the subject the tools traditionally applied to the study of other diseases—a careful description of the different forms of iatrogenic disease, an identification of pathogenetic mechanisms, and an examination of possible preventive measures.*

LAWRENCE M. TIERNEY, Jr, MD†: Iatrogenic illness has long been recognized by physicians, the initial observation of this phenomenon being credited to Hippocrates. The word *iatrogenic* in the strictest sense means "causing physicians"; a term such as "iatrous" might be more appropriate for describing diseases caused by physicians, but the former term has long been established and will likely remain in common usage. That Hippocrates recognized that an adverse outcome from the physician-patient interaction was a possibility indicates that this problem is as ancient as medicine itself. For purposes of this discussion, iatrogenic will refer to illness caused not only by physicians but by patients' interactions with the health care system generally, including those problems that are not directly caused by physicians' errors.

The Scope of Iatrogenic Disease

It is surprising that so little is known systematically about the incidence and prevalence of iatrogenic disease. The best observations of iatrogenic disease have taken place in intensive care populations in whom physician error is more likely to be obvious and thus stand out to external observers.[1] Similarly, patients in intensive care units often have many complex problems and require high-risk procedures and therapies,[2] all of which lead to the likelihood of iatrogenic problems occurring. Most of medicine, however, is practiced in settings outside the intensive care unit, and most care delivery takes place in outpatient settings. There is probably not a single detailed review of iatrogenic events in this venue. A few interesting articles have analyzed non-intensive care inpatient iatrogenic illness but none recently.[3,4] At the same time, there have been hundreds or even thousands of individual case reports and the occasional small series[5,6] of specific iatrogenic events; for the most part, these describe an adverse outcome from a diagnostic procedure[7] or therapeutic intervention.[8] Though useful, this type of information does little to provide an overall view of the scope of the problem, though it does define certain specific issues. In this discussion, iatrogenic illness will be viewed much as any other medical condition: namely, as a problem that has distinct clinical expressions, causes, and treatments. Looking at iatrogenic illness in this way allows a more comprehensive approach to the problem and could potentially produce a framework for more systematic studies in the future.

Types of Iatrogenic Illness

The clinical expression of iatrogenic illness may be divided into approximately five major groups. The first of these is the most obvious: direct bodily harm related to diagnostic, invasive therapeutic, or supportive procedures. Obvious examples include pneumothorax induced by thoracentesis, dissection of a coronary artery at angioplasty, and other similar mishaps. These are usually evident to a clinician, and, indeed, for most such procedures, the anticipated incidence of the complication in question has been established, such as the mortality and morbidity figures for various surgical procedures.

The second clinical type of iatrogenic disease is the organ-specific or systemic insult resulting from pharmacotherapy. Adverse reactions to drugs may be dose-related, idiosyncratic, interactive, or merely the expected effect of the therapeutic agent. A seizure occurring in the context of penicillin therapy is dose-related; aplastic anemia resulting from chloramphenicol use is idiosyncratic; a barbiturate-induced reaction in a patient taking warfarin sodium is interactive; and the neutropenia from the use of antineoplastic drugs may be considered an expected effect. During the past two decades, there have been many advances in the understanding of drug effects, particularly interactions, and this is obviously an important step in understanding iatrogenic medicine, given the average number of medications taken both by inpatients and outpatients in internal medicine practices.

A third, and uncommon, expression of iatrogenic illness is the emergence of a "new" disease as an indirect and unex-

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pected consequence of previous therapy.[9] An example is the development of acute leukemia many years after aggressive and often curative therapy for lymphomas. A fourth clinical example might be called "passive" iatrogeny: physicians allowing the natural history of disease to progress untreated. An example here is the withholding of antibiotic therapy until the results of cultures have been obtained in febrile patients who ultimately prove to have bacteremia. Though neither an active or obvious problem, this can certainly be considered iatrogenic. The final expression of iatrogenic illness is one that extends the definition noted earlier; this is an insult unrelated to the process of care giving. An example is a patient who falls out of bed while in the hospital. Though not iatrogenic in the strictest sense, this constitutes an extremely important problem, at least in inpatients, and may account for upward of a fifth of inpatient iatrogenic episodes.

Pathogenic Mechanisms

If this constitutes a broad but superficial "clinical classification" of iatrogenic illness, specifying *how* these events occur, it is then useful to probe more deeply and to consider *why* they happen—that is, to identify causes. Even a cursory inspection reveals that this is more important to understanding iatrogenic illness than the clinical expression itself, as is true throughout the practice of medicine. An example of a medical condition with multiple causes that results in a similar clinical expression is hepatitis; the treatment of hepatitis—and, by analogy, of iatrogenic illness—requires that the cause be understood. Iatrogenic events, irrespective of the how or why, take place within the usual clinical sequence of history, physical examination, diagnosis, and treatment. Many of their causes, therefore, are traceable to the process of educating students and house officers, and many may be ascribed to human characteristics shared by all who practice medicine.

Clearly we can start with the clinical history. Though a comprehensively taken history is the most important part of the physician-patient interaction resulting in a diagnosis, this tenet is honored more often in the breach. A detailed medical history requires a proper balance of using what has happened to a person in the past—particularly if this type of information is objective—with current and firsthand, subjective information obtained from the patient. Objective data are typically found in old records that the physician may have or that may be in other locations. A failure to review these or to make an effort to find previous studies may result in an iatrogenic illness. For instance, it should be considered a matter of proper history taking in a patient with a solitary pulmonary nodule to review a previous chest x-ray film; a pneumothorax resulting from a needle biopsy, an iatrogenic injury, would have been avoided if a previous film showing the same abnormality had been found.

Other aspects of the medical history that frequently lead to iatrogenic problems include labeling. If patients are erroneously characterized in medical records as hypertensive or diabetic, they receive more medications, have more visits to physicians, and, indeed, lose more days of work than patients not so identified. Proper history taking should mitigate the results of labeling. Other labels that result in problems for patients include the psychiatric; often, passive iatrogeny may occur in a psychiatric patient whose care givers may not believe the validity of current symptoms because of the psychiatric diagnosis. Recently it has been observed that a label of positivity for the human immunodeficiency virus (HIV) can result in numerous assumptions about a patient that can lead to harm. This can even occur in patients wrongly assumed to be HIV-positive because of the presence of a potential risk factor. Rigorous history taking would avoid this.

A subset of iatrogeny stemming from the medical history is a reduction in the scope of the history obtained, sometimes resulting from a failure to seek out family members or previous physicians. Questions may need to be asked repeatedly; patients may need to be stimulated to remember important items about their past, particularly if they think of them as irrelevant to their current problem. Thus, the history is often the root cause of one of the types of iatrogenic illness.

Another cause, albeit a less common one, of iatrogenic harm is in the physical examination. On rare occasions, this results in direct injury to a patient. More often, the failure to appreciate a physical sign when present can be harmful. Third, and perhaps of most consequence, is a falsely abnormal (false-positive) finding. Examples of each of these phenomena include, respectively, splenic rupture from repeated palpation in a patient with mononucleosis, a failure to hear a diastolic murmur, and, as an example of a falsely abnormal finding, the belief that an abdominal mass is present when it is not. Each of these in its own way can hurt a patient, but each is different. In the first instance, there is direct injury to the patient; in the second, a delay in diagnosis, or passive iatrogeny; and, in the third, exposure to unnecessary diagnostic studies, with a possible direct injury to the person tested.

One of the most common causes of the expression of iatrogenic illness originates from the ill-conceived or inappropriate use of diagnostic tests. This applies to studies such as blood chemistry tests and, more obviously, to the increasingly complicated diagnostic studies in use in the late 1980s. In examining how clinicians use diagnostic tests, we find several possible subsets as concerns iatrogenic illness. A classic example is an incidental abnormal finding on a "routine" chemistry panel, ostensibly done for screening purposes. In many instances, physicians ordering such studies do not understand the proper definition of screening, nor are they aware of the concepts of specificity and sensitivity, although in fairness much more attention has been given to these concepts in recent years. Nevertheless, an incidental false-positive test can be damaging to a patient.

All laboratory studies use a population of healthy persons to define the range of results on a given test; because the normal range is defined as the mean plus or minus two standard deviations, 5% of such a normal population have "abnormal" results. Simple mathematic calculation, then, indicates that on a 12-test chemistry panel, any healthy person has at least a 50% chance of having one "abnormal" value. Depending on the test result that is abnormal, further diagnostic studies are frequently initiated. For instance, an elevated alkaline phosphatase level, even in a clinically healthy person, frequently results in an imaging procedure of the abdomen. This latter, particularly if it is an abdominal ultrasonogram, examines more than just the liver and biliary system. There are few clinicians who have not been surprised by unexpected findings on such studies. One could argue that this occasionally benefits a patient; more often, the opposite is true. Thus it becomes crucially important for physicians to be aware that so-called abnormal laboratory findings are an everyday occurrence in healthy patients. The ill-conceived

use of laboratory studies as a screening device is certain to have potential for harm.

It also should be pointed out that in many academic medical centers, where residents are responsible to attending physicians, there is a tendency to order numerous tests in the interest of appearing compulsive or to document that thought has been given to many diagnostic possibilities. Many attending physicians promulgate this behavior by harkening back to the days when such a level of compulsivity was de rigeur.

Still another mechanism that is apt to initiate a false-positive test is the widespread penchant of patients, particularly in this country, to insist on a panoply of diagnostic studies on a regular basis as a part of health maintenance. When combined with the fear of litigation common in practicing physicians, an obvious scenario results in which false-positive diagnostic studies are not only obtained but pursued with other diagnostic studies as described earlier. Mold and Stein have referred to this as the cascade effect,[10] an apt characterization. This cascade effect is prominent in asymptomatic patients but may be applicable in different ways to patients with unexplained symptoms and particularly to patients who are seriously ill. In those instances, increasingly invasive studies, with a diminishing likelihood of a diagnostic return, are often carried out. An example is the routine use of an exercise thallium stress test and cardiac catheterization in patients with chronic stable angina, for fear of missing left main coronary artery disease or severe triple-vessel-equivalent disease. Another example noted in intensive care units is transbronchial biopsy or even open-lung biopsy in patients with the adult respiratory distress syndrome. This is not to suggest that these tests are contraindicated in all instances; rather, it points out that as the complexity of diagnostic studies increases, there is an increase in the risk of harm. A 12-panel chemistry study could hardly be considered "invasive," but if that study reveals an elevated alkaline phosphatase level that ultimately results in an unindicated cholecystectomy with postoperative complications, it might be hard to convince the patient that it was not invasive.

None of these concerns about diagnostic tests address the issue of technical error, which is aggravated by inexperience. Many of the "smoking guns" that clinicians recall as gross examples of iatrogenic injury fit into this category. This type of mishap is often encountered in the training setting, and though such problems may be the acknowledged result of inexperience, they are worsened when inexperience itself changes the indications for a diagnostic procedure. It would be of interest, for example, to study whether there is a change in the frequency of various diagnostic studies, such as thoracentesis or lumbar puncture, in teaching hospitals at times of the year when medical students are on vacation. Further, technical error is made more likely by the increasingly complicated array of diagnostic and therapeutic procedures now performed in medicine. Again, there may be considerable benefit from doing these procedures, but it remains the duty of physicians to strike the proper balance between their risks and benefits in particular situations. It is worthwhile to remember that though technical mishaps on complex procedures stand out in bold relief to the day-to-day practice of medicine, it is often a "noninvasive" study that initially brought a patient to a more complicated procedure.

Finally, though it is probably less common these days, the omission or delay of an indicated study may be every bit as harmful to a patient as what has been described here. This passive iatrogeny may have its roots in many mechanisms, including physician ability, problems with medical record keeping, and the like, but it is not to be ignored. On balance, however, diagnostic studies result in iatrogenic harm to patients far more often by their overuse than by their underuse.

Still another cause of iatrogenic illness relates to the gaps in diagnostic synthesis that take place in the practice of medicine. Clearly all of us could stand to know more pathophysiology, pharmacology, and the like, and much is made of the explosion of biomedical information that overwhelms clinicians trying to care for patients. Although all of us would like to be more widely read or knowledgeable, it seems unlikely that an overt knowledge deficit contributes to many iatrogenic problems; more often, it is how the existent knowledge is used.

A greater problem in arriving at the proper diagnostic synthesis relates to a failure to assign the highest priority to remediable conditions. There is a certain amount of allure, particularly for internists, in the diagnostic process itself, and, commonly, their egos are involved in the desire to be accurate. Nevertheless, attention to treatable conditions in the differential diagnosis is more beneficial to patients, even if probabilities might dictate otherwise. For instance, even if bacterial endocarditis seems much less likely than a malignant neoplasm or a bland embolic stroke, approaching a case as though the former is operative is much less likely to result in harm.

Just as diagnostic studies may injure patients, so may therapies, and this has already been referred to as one of the direct clinical expressions of iatrogenic illness. Certain parallels may be drawn between therapeutic iatrogeny and diagnostic iatrogeny. The most obvious of these concerns the adverse outcomes from drugs prescribed for marginal indications, when toxic effects result from the administration of an agent not indicated in the first place. This might be considered analogous to harm coming from the cascade originated by the incidental finding on diagnostic studies. In recent years, increasing sophistication in clinical pharmacology has led to more awareness of drug interactions on the part of clinicians and has also reduced the incidence of occasional errors resulting from gross misdosing.

Another similarity between diagnostic and therapeutic misadventures occurs in the invasive therapies that we have in our armamentarium. On many occasions, the therapy is applied at the same time as the diagnostic study, the best example being angioplasty. Nevertheless, the concept remains the same. Invasive or interventional therapeutic techniques, when they result in a mishap, have the advantage of showing immediate cause and effect, and they are often associated with striking clinical events. There is no conceptual difference, however, between this type of toxicity and the more delayed problem that occurs as a consequence of the inappropriate use of a prescription drug. The rupture or dissection of a target artery at angioplasty is at once striking and frightening; the outcome for the patient, however, is similar for something like isoniazid-induced hepatitis. In either instance, clinicians should be aware of the incidence of toxicity and should take it into account in prescribing the therapy initially.

Another important cause of iatrogenic events is the assumption of the innocuous nature of the process of care. It has been pointed out that an insult unrelated to the process of

care accounts for a fairly large percentage of clinically expressed iatrogenic events.[11,12] These events might be less likely to occur if the process of care were taken more seriously. Admission to hospital for any reason carries with it many risks, and "supportive" care is particularly troublesome. Two excellent examples of the latter are sepsis related to intravenous catheters and urinary tract infections caused by indwelling catheters. Both are eminently avoidable; they nevertheless occur commonly. This likely results in part from the long-standing assumption that merely because a patient is in a hospital and receiving care, no harm will come from the process itself but rather from diagnostic and therapeutic events. This, unfortunately, is not the case.

Inherent in all of these causes of iatrogenic illness, and also standing as a separate cause, are the sociologic factors relating to the training of house officers. Medical expertise through apprenticeship has obvious historical standing, and physicians have all learned much from mentors throughout their careers. The concept of apprenticeship, however, is more appropriate to a trade than a profession, and overemphasis brings the potential for harm, particularly given the complexity of modern medicine. The phrase "see one, do one, teach one" is well known to everyone who has done residency in any specialty and, indeed, is well established in the lingo of third-year medical students. This argot might have had some legitimacy when venipunctures and similar simple procedures were the rule of the day; it is far less valid in 1989 when pulmonary artery catheterization and techniques like it are regularly carried out. With complex procedures, few physicians in training do enough to be truly competent. There, nevertheless, remains the urge to learn how to do them, perhaps because the mastery of certain techniques stands as a validating rite of passage in learning to be a physician. The potential for harm now requires a more thoughtful appraisal of this epithet.

Another sociologic phenomenon causing indirect but palpable harm to patients is the intrinsic reward system that remains a seemingly immutable part of medical training programs. Peer evaluation within residency cohorts tenders high esteem toward members of the group who have apparently mastered the medical literature; the ability to quote the essence of a recent paper is much more highly praised than knowing how to use the information gleaned from it. Similarly, there is a nearly irresistible tendency to apply newly learned information, often in an uncritical fashion. There are numerous examples of how this can result in harm to patients. Yet another social phenomenon that may affect patient care, again within peer groups, is the behavior of admitting residents in an emergency department. Few students or residents would have any difficulty recognizing that the term "rock" is positive and praiseworthy and that the term "sieve" is pejorative. Current fiscal constraints and the shift of much evaluation of patients into ambulatory settings complement this dangerous attitude. Obviously these characterizations are closely related to the workload on inpatient services, which is largely dictated by the patients admitted from the emergency department. Though it is clearly not an active or meaningful attempt on the part of trainees to increase patient discomfort and, in general, is a characterization tendered in a patient-neutral setting, this type of peer evaluation can affect the admitting policies of an emergency department resident and, thus, may result in considerable harm to patients.

From this type of observation, it is a short move into still other sociologic causes of iatrogenic illness, namely stress and fatigue. It is unfortunate that it has taken a number of adverse physician-patient interactions over a great many years before these universals of training have been given the attention they deserve. Both stress and fatigue inarguably impair judgment, hamper the physician-patient relationship, and damage students' and residents' attitudes toward medicine.

Other sociopolitical events can also result in harm to patients; even a well-rested house staff that is dealing effectively with stress may be no match for the problems created by the reduction in resources and the increased expense of medical care. The medical profession might argue that it is not responsible for addressing this fundamentally political problem, but a more positive approach might be to recognize that social and political barriers placed between patients and physicians are indeed relevant and without doubt result in harm to patients.

Still other social causes of iatrogenic illness include cross-cover policies by on-call physicians. Few would disagree that far more procedures and therapies are applied to patients in whom new problems develop when their primary physicians are unavailable. This is well intended to minimize the subsequent work of the resting colleague but may result in harm to patients by the mechanisms described.

A final thought on the social causes of iatrogenic illness relates to society at large because the medical profession can only be a reflection of its society. Our society is one that favors action over observation. Numerous diagnostic procedures and therapeutic interventions in widespread use have not been proved critically to be beneficial for patients; nevertheless, the desire on the part of both patients and physicians to "do something" is a forceful one and drives the development of new diagnostic and treatment strategies and procedures. This is not to eschew increasingly sophisticated technologies or their application to sick patients; it is, rather, to point out that everything new, just as everything old, has its price and that those who practice medicine must be aware of this.

The increasing subspecialization of medicine is yet another cause for iatrogenic events. This might logically be described as a diffusion of responsibility, and though it is observed often in private practice, it is of particular importance in training institutions, especially those with more than one hospital. In these instances, no care giver is entirely certain who bears the overall responsibility for a given patient, whether in the inpatient or the outpatient setting. This results in a repetition of tests, increasing the chance for false-positives, in actions based on a preexistent abnormality that had been investigated previously, and even in some passive iatrogeny, based on the assumptions that certain studies or procedures would certainly have been done on a given patient and thus need not be repeated.

Finally, it should be recognized that Murphy's Law operates in medicine as in all other systems and that simple bad luck may occasionally result in harm coming to patients. Clinicians may take thorough histories, conduct professional physical examinations, do the correct studies, and prescribe the indicated treatments, and adverse events will still occur. Everyone who has ever practiced medicine, or who for that matter engages in any human endeavor, understands this concept. It is important that these inevitable untoward events not

affect the approach to medical practice of the clinicians so victimized.

Preventing Iatrogeny

It can be seen that the root causes of iatrogenic injury—and no doubt there are many more—are much more subtle than their final clinical expressions. If there is the wish to devise "treatment," as for any other "disease," it is critical to identify the original cause; therapy for an individual episode, though appropriate and indicated, does not address the overall problem in any useful way. What, then, are the concepts of "treatment" that might apply to iatrogenic illness?[13,14] To deal first with Murphy's Law, in contrast with the Hippocratic dictum of "first, do no harm," it is clear that overreaction can lead to an antonymic "last, do no medicine." As has been pointed out, passive iatrogeny may be as harmful as the active form, and physicians must be temperate in approaching possible iatrogenic illness of patients.

Several tenets may be useful in a systematic approach to iatrogenic illness. First, clinicians must be rigorous in their use of diagnostic studies. Action, or a lack of action, should be prospective and not reactive. Diagnostic studies should be done to test a hypothesis, not just to look for some unspecified abnormality or to "treat the chart." This same prospective analysis applies as much to the chemistry panel as it does to coronary angiography or an open-lung biopsy; if it will not change what the clinician does, there is no point in pursuing it. In a certain sense, the term "noninvasive" may be misleading in this regard. Surely no test can be considered noninvasive if it is the proximate cause of further, more invasive studies that have the potential to harm a patient. Perhaps "preinvasive" would be a better term, although it is unlikely to attract many advocates.

Another fundamental aspect of the therapy for iatrogenic illness resides in the reward system in place in medical training settings. This addresses many of the sociologic phenomena referred to earlier but is also at play in many other causes as well. Much lip service is paid during residencies to the importance of excellence in fundamentals: namely, a careful history, a meticulous physical examination, and a scholarly differential diagnosis. Nevertheless, few external rewards are given for skills in these disciplines. Physicians too seldom praise their colleagues for excellence in these activities, in striking contrast to the comments about the behavior of emergency department residents in acting as sentinels to inpatient service. Responsibility for this reward system lies with those who structure student clinical clerkships and the content of residencies. Another important part of altering the reward system in training is the crucial need to de-emphasize technical expertise as an end in itself. The traditional apprenticeship concept tends to promulgate this; if iatrogenic events are to be avoided, one way to do so would be to reward knowing *when* to do a procedure rather than how. If any technical procedure can be mastered readily by someone without any formal training in medicine, it does not deserve an important role in the medical schools and residencies. Finally, as regards the reward system, it has been gratifying to observe the mounting interest in stress and fatigue as operant conditions in unnecessary patient injury; it can only be valuable to all if residents no longer feel pressure to conform to the "days of the giants" concept of what constitutes an appropriate workweek for a physician in training.

Another form of treatment critical in avoiding iatrogenic illness is the maintenance of a healthy level of skepticism regarding new developments in medicine. As has been repeatedly noted here, physicians, and indeed their patients, are attracted to new technologies for many reasons. Many things that are standard practice in medicine remain unproved in any rigorous way and have been applied to patients only because of their theoretic value and early anecdotal reports of success. It should be a major responsibility of academicians to require proof of efficacy for procedures in widespread use. The requirements by the Food and Drug Administration for the use of a new drug are a striking contrast to this.

Still an important part of treatment is the legitimacy of empiricism in medicine, as contrasted to that which has been established beyond doubt as efficacious for patients. I do not contend that empiricism has no place, for many strategies have emerged in this way and contribute to the proper care of patients. A healthy skepticism simply requires the recognition on the part of physicians as to what is proved and what is unproved and persistence in demanding accurate information on the nature of the proof. Another treatment modality might be summed up in the gatekeeper approach to highly technical care that has been espoused by Eisenberg.[15] This approach limits access to highly technical diagnostic and therapeutic procedures, with the "gate" to these procedures being regulated by a primary care physician. Though no doubt this approach would be considered draconian by many, there is little argument that it offers great potential benefit for patients. The imbalance between the provision of primary care and specialty care needs to be redressed, however, before a comprehensive adoption of this therapy can be advocated. Other preventive measures for iatrogenic disease, such as reducing the length of hospital stays, have already been applied throughout the country, although largely for economic reasons rather than to reduce the risks of injury to patients. Another measure is continuing the effective monitoring of diagnostic and therapeutic methods. An administrative insistence on quality assurance in many care settings may help in this regard, although more often this type of monitoring addresses specific clinical expressions of iatrogenic illness, rather than dealing with any of its causes. Finally, it is critical to recognize that medicine is a healing art practiced by human beings. That all humans have failings applies as much to physicians as to persons in any other walk of life. It is crucial for those who practice medicine to keep this simple fact in mind and to maintain a high index of suspicion that an adverse event may be related to the process of care itself rather than to the disease requiring care.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Rehabilitation of the Physically Disabled Adult

Edited by C. John Goodwill, MB, BS, FRCP, Consultant Physician in Rheumatology and Rehabilitation, Kings College Hospital, London, and M. Anne Chamberlain, BSc, FRCP, Consultant Physician in Rehabilitation Medicine, General Infirmary at Leeds; Honorary Senior Lecturer, School of Medicine, University of Leeds; and Director of the National Demonstration Centre in Rehabilitation, Leeds. Sheridan House Inc, 145 Palisade St, Dobbs Ferry, NY 10522, 1988. 852 pages; $89.50 (cloth), $45 (paper).

The sensitive and thought-provoking chapters in *Rehabilitation of the Physically Disabled Adult* embrace a broad spectrum of viewpoints on various disabling conditions and provide a fascinating and often shocking insight into the workings of British society and the National Health Service.

Arranged systematically according to musculoskeletal, energy-restricting, sensory, communication, and neurologic disorders, contributors include specialists in rehabilitative medicine, rheumatology, orthopaedics, neurology, dental surgery, geriatrics, pediatrics, ophthalmology, audiologic medicine, cardiology, plastic surgery, epidemiology, and community medicine. Additional chapters by allied health professionals, a medical physicist, and a rehabilitation engineer are included on select topics such as incontinence, sexual dysfunction, adaptive equipment, bioengineering, social services and benefits, housing and residential care, education, and employment.

The picture that emerges is of a society with a long and proud tradition of providing caring, supportive services to "invalids," but which is struggling to develop those attitudes and technologies that enable citizens with disabilities to become independent and productive members of society.

To an American physician like myself who has been sensitized to empower persons with disabilities to reach for what were previously considered to be unattainable goals—white water rafting, climbing a mountain in a wheelchair, marathon racing, playing wheelchair racquetball, scuba diving despite blindness or paralysis—it is rather shocking to read that recreation for spinal cord injured patients must be "limited to gardening and *possibly* birdwatching (emphasis mine)," or that "He can fish, providing the wheelchair is suitably anchored so that the fish does not win." Paternalistic, old-fashioned, and overprotective attitudes like these compromise the authors' basically sound medical information on the pathophysiology, diagnosis, and treatment of disabling conditions.

Yet, juxtaposed among linguistic and clinical anachronisms such as the term "Invalidity Pension" (after all, who is an invalid? One without rights or responsibilities!) and medical recommendations such as to consider hysterectomy or radium-induced menopause for women confined to wheelchairs since they are "irked by menstruation," there are descriptions of progressive and innovative programs for enhancing self-sufficiency and quality of life. Despite "problems with organization of care in the National Health Service, lack of interest by doctors, insufficient psycho-social support, long delays in the supply of equipment such as wheelchairs which may be unsuitable when they do arrive," the National Health Service provides sophisticated electronic environmental control and communication systems for which most Americans have neither private nor government funding. Those with mobility impairments are entitled to a Mobility Allowance, which they can use as they please: to purchase or lease a vehicle, pay for taxis or transportation for vacations, or to reimburse the expenses of friends who give them rides. Voluntary organizations negotiate for disabled consumers so they can purchase cars, vans, electric wheelchairs, assistive devices, and insurance on a wholesale or discount basis. What great ideas!

The book is the work of mature, thoughtful clinicians. Its dispassionate description of the medical impairments and societally generated handicaps faced by adults with various disabilities is a challenge to physicians and other rehabilitationists on both sides of the Atlantic to work together to improve the organization, coordination, and funding of private and government health and social services so that our patients/clients can have equal access and equal opportunities in a global society in which dreams can become realities.

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Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under its direction.

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Fungal Sinusitis in Immunocompetent Patients

SINUSITIS is a common problem in otherwise healthy persons, especially those with atopic disease. The most common etiologic agents are bacteria and viruses. Less commonly, sinusitis may be caused by a variety of fungi. Fungal sinusitis in an immunocompromised patient is often a fulminant life-threatening disease and is most commonly caused by *Aspergillus* species or the agents of mucormycosis (zygomycosis). In an immunocompetent patient, fungal sinusitis is usually chronic and is diagnosed when surgical treatment is carried out in patients who have not responded to antimicrobial therapy for presumed bacterial sinusitis. Therefore, the possibility of fungal sinusitis should be considered in patients with sinusitis unresponsive to appropriate antibacterial therapy.

Three categories of fungal sinusitis have been described: invasive, chronic noninvasive, and allergic. Invasive disease is characterized by local extension with necrosis of soft tissue and bone and most commonly occurs in immunocompromised patients. Noninvasive sinusitis is typified by the presence of a "fungus ball" in one or more of the paranasal sinuses. A local inflammatory response without tissue destruction results. *Aspergillus* species are the most common causes of noninvasive fungal sinusitis. The diagnosis and treatment of this condition are primarily surgical; antifungal therapy probably has no role. Allergic sinusitis is also caused primarily by *Aspergillus* and is found in patients with asthma and recurrent sinusitis. Histologic examination of the sinuses reveals mucus containing fungal hyphae as well as eosinophils and Charcot-Leyden crystals. Whether this disorder is distinct from noninvasive sinusitis is not completely established.

More recently, the dematiacious (pigmented) fungi have also been associated with sinusitis. These include *Bipolaris* (formerly called *Drechslera* or *Helminthosporium*), *Exserohilum, Curvularia,* and *Alternaria.* Patients frequently have atopic disease, such as hay fever and nasal polyposis, but are otherwise healthy. The most common symptoms are chronic nasal discharge or obstruction that has not responded to antibacterial agents or nasal corticosteroids. Sinus radiographs and computed tomography show sinus opacification without an air-fluid level. A computed tomographic scan sometimes shows local bony destruction. Fungal hyphae are found in the mucus from surgical specimens and, less commonly, bone invasion, necrosis, or both are found. Thus, this disorder overlaps all three classes of fungal sinusitis mentioned earlier. Although primarily a noninvasive disease, there may be local invasion, and patients frequently give a history of allergic symptoms. The prognosis is variable. In a few patients, cerebral extension develops despite surgical and antifungal therapy. Some have required several surgical procedures to stabilize their disease, but others have apparently been successfully treated with a single surgical procedure.

Until more is known about the natural history of sinusitis caused by the pigmented molds, these patients should probably be treated with antifungal therapy in addition to surgical debridement. Amphotericin B is the most effective agent currently available, and ketoconazole has some in vitro activity. Itraconazole, an investigational triazole, shows good in vitro activity against these fungi and may prove to be a satisfactory oral agent for treating patients with chronic fungal sinusitis.

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Continuous Estrogen-Progestin Therapy in Postmenopausal Women

ESTROGEN REPLACEMENT THERAPY in postmenopausal women has been widely advocated for the relief of climacteric complaints and the prevention of osteoporosis. In addition, the use of standard doses of conjugated estrogen (0.625 mg) has been shown to increase high-density-lipoprotein (HDL) cholesterol levels by about 15% and is associated with a relative risk for cardiovascular disease of 0.2 to 0.7 com-

pared with that of nonusers. At present, contraindications for postmenopausal estrogen replacement are personal history of breast cancer, endometrial cancer, or deep venous thrombosis. An adverse effect of estrogen therapy is endometrial hyperstimulation, which can lead to hyperplasia and eventually carcinoma. The relative risk estimates for endometrial cancer associated with estrogen replacement range from 2 to 12, depending on the duration of estrogen use and the cumulative dose. The incidence of endometrial hyperplasia in patients receiving continued unopposed estrogen therapy is 15% to 50%, but this can be reduced to zero if progesterone is added for at least ten days each month. The duration of the progestin treatment each month is more important than the dose in preventing endometrial hyperplasia. The progestational side effects appear to be more dose-dependent and include symptoms like abdominal bloating, headache, depression, and acne. Another serious effect is a reduction in the beneficial effect of estrogen on the HDL cholesterol.

A standard regimen for hormone replacement therapy has been the cyclic administration of estrogen and progestin. A new approach has recently been introduced involving the use of continuous combined treatment. Four studies have looked at the daily use of estrogen—conjugated equine estrogen, 0.625 mg, or estradiol valerate, 2 mg—and a low-dose progestin, such as medroxyprogesterone acetate, 2.5 to 5 mg, or norethindrone, 0.35 to 2 mg, in 148 postmenopausal women observed for 3 to 18 months. These treatments were consistently shown to produce amenorrhea with an inactive endometrium, while alleviating climacteric symptoms. The amount of breakthrough bleeding tended to decrease with the increasing doses of progestin used. Most of the bleeding occurred during the first four months of treatment, and by the ninth month spotting was uncommon regardless of the dose used. It is reassuring that despite breakthrough bleeding, no endometrial hyperplasia was found during continuous treatment in any of the women studied. Two short-term trials using daily conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg, showed either no change in lipoprotein levels or a statistically significant decrease in total and low-density-lipoprotein cholesterol levels from pretreatment values.

The optimal formulation for daily hormonal therapy in postmenopausal women is still unknown. It seems reasonable to initiate treatment with one of the combinations already studied, like conjugated estrogen plus low-dose medroxyprogesterone acetate. After several months the progestin dose may be adjusted, either downward to the lowest dose that maintains amenorrhea, or upward if breakthrough bleeding occurs. If bleeding persists on a higher dose, it would be prudent to do a gynecologic evaluation and possible endometrial biopsy. If breakthrough bleeding is minimal after a few months of treatment, standard guidelines for routine pelvic examinations and Pap smears could be followed. If larger studies continue to show a complete suppression of endometrial proliferation on continuous combined therapy, there should be no need to do regular endometrial biopsies on these patients. There are many other issues to be considered in the management of perimenopausal women who still have cyclic bleeding, but these will not be discussed here.

In summary, the use of a daily combination of estrogen with a very-low-dose progestin may be an easy, convenient, and safe way to provide hormone replacement in postmenopausal women. This treatment seems preferable to conventional therapy because it avoids cyclic bleeding and reduces progestational side effects while protecting the endometrium. It may also prevent the climacteric symptoms that some women experience during the period of estrogen withdrawal. Larger long-term studies are still needed to document that the benefits of adding continuous low-dose progestin to estrogen replacement outweigh the risks.

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Ganciclovir for Cytomegalovirus Retinitis

RETINITIS IS the most common manifestation of cytomegalovirus (CMV) disease in immunocompromised patients, especially those with the acquired immunodeficiency syndrome (AIDS). Although CMV infection can cause disease at other sites, such as the esophagus, colon, and central nervous system, the retina is the most commonly involved site in patients with AIDS. Although CMV infection is an unusual index AIDS diagnosis, this infection will develop in 5% to 10% of patients at some time during the course of the disease. Lengthened survival due to improved antiretroviral chemotherapy and the suppression of *Pneumocystis carinii* pneumonitis will doubtless increase the incidence of other opportunistic infections such as CMV.

Ganciclovir has recently been approved by the Food and Drug Administration for the treatment of life-threatening CMV retinitis. It is a nucleoside analogue like acyclovir. Clinical trials with ganciclovir began in 1984, and clinicians (especially those caring for AIDS patients) quickly came to the conclusion—in the absence of prospective, comparative studies—that the drug was effective. It was not until several years later, however, that a series of prospective and retrospective clinical trials provided convincing evidence of efficacy.

Ganciclovir is currently recommended for the treatment of sight-threatening CMV retinitis. Patients with this disease have visual symptoms, and retinoscopy shows the typical changes of CMV retinitis—perivascular hemorrhages and whitish "exudates" (actually, necrotic retinal tissue). Asymptomatic patients with rapidly progressive retinitis moving toward the macula may also warrant treatment. Therapy for patients with asymptomatic, nonprogressive or slowly progressive peripheral CMV retinitis or those with end-stage (blinding) retinitis in one eye is still controversial. It is not yet clear that the benefits of long-term ganciclovir therapy exceed the risks of toxicity in such patients.

Treatment with ganciclovir is traditionally divided into two phases: the initial treatment phase—usually called the "induction" phase, by analogy with cancer chemotherapy—and the later phase of long-term chemosuppression, usually called the "maintenance" phase. The drug is always given intravenously. The induction dose is 5 mg per kg of body weight given every 12 hours for 14 days; the dose needs to be reduced for patients with renal insufficiency. All patients receiving induction should be placed on a maintenance

dose of the drug, the risk of relapse being virtually 100% for those not treated; most experts recommend 5 to 6 mg per kg a day, given once daily five to seven days per week. Both the latter part of the induction phase and the maintenance phase can be given at home. Patients should be monitored fortnightly by an ophthalmologist.

The principal toxic effect of ganciclovir is neutropenia. Dose-limiting neutropenia will develop in about 10% of patients during induction and in 20% during the maintenance phase. We recommend discontinuing therapy if the absolute neutrophil count falls to 500×10^6 per liter. After the granulocyte count returns to baseline, many patients can tolerate a reduced dose. Synergistic toxicity with zidovudine (AZT) is nearly universal, and only a small proportion of patients will be able to tolerate even reduced doses of AZT with maintenance ganciclovir. Other adverse effects, such as thrombocytopenia, hepatitis, eosinophilia, nausea and vomiting, confusion, and rash, are less common and are rarely dose limiting.

As the first drug effective against CMV disease, ganciclovir is a major therapeutic breakthrough, but it is toxic, dose-limiting adverse reactions are common, and it must be given by intravenous infusion. Therapy with this drug should therefore be reserved for patients with sight-threatening CMV retinitis.

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Monitoring Sodium Warfarin Therapy Using the International Normalized Ratio

THE PROTHROMBIN TIME (or prothrombin ratio), the time-honored test used to monitor the anticoagulant effect of sodium warfarin therapy, is gradually being supplemented or replaced by a new measure, the international normalized ratio (INR). The use of the INR is being adopted because the thromboplastin reagents used in different laboratories to measure the prothrombin time may have significantly different sensitivities to warfarin-induced changes in vitamin K-dependent clotting factors. The prothrombin time results from two different laboratories on a single specimen of plasma may show a difference in the measurement as great as two to three seconds! Thus, a patient who has an apparently "therapeutic" prothrombin time measurement in one laboratory may have a nontherapeutic prothrombin time result in a different laboratory.

Conceptually, the INR standardizes prothrombin time measurements by taking into account the sensitivity of the thromboplastin reagent being used. Mathematically, the $INR = (PR)^{ISI}$, where the PR is the prothrombin ratio—a patient's prothrombin time divided by the control prothrombin time—and the exponent is the international sensitivity index (ISI) of the reagent. Thus, the INR is identical to the prothrombin ratio when the ISI is 1.0. In Great Britain, where human brain thromboplastins are used, the ISI values are close to 1.0, but in the United States, where rabbit brain thromboplastins are used, ISI values are notably higher, in the range of 1.9 to 2.6.

Recently published guidelines for managing oral anticoagulant therapy define optimal therapeutic target ranges using INR units. Most thromboembolic disorders can be successfully treated using "low-intensity" oral anticoagulation therapy, with the INR between 2.0 and 3.0. These conditions include the treatment of deep vein thrombosis and pulmonary embolism; the prevention of venous thromboembolism in patients undergoing a high-risk surgical procedure; and the prevention of systemic embolization in patients with tissue heart valves, valvular heart disease, atrial fibrillation, and after an acute myocardial infarction. "High-intensity" anticoagulation therapy, with the INR between 3.0 and 4.5, is necessary to prevent systemic embolization in patients who have a mechanical prosthetic heart valve and to treat patients who have a thromboembolic complication while on low-intensity therapy.

If a clinical laboratory does not provide the INR value with each prothrombin time, it is possible to determine it by requesting the ISI value of the thromboplastin reagent and finding the INR value on a published nomogram. (The INR value can also be easily calculated using a pocket calculator equipped with logarithmic and exponential functions.) If the ISI of the thromboplastin reagent is unknown, there is no way to calculate the INR value. Assuming that a thromboplastin reagent has an ISI value of 2.4 and that the control prothrombin time is 12 seconds, the low-intensity INR range of 2.0 to 3.0 is equivalent to a prothrombin time between 16 and 19 seconds, and the high-intensity INR target range of 3.0 to 4.5 is equivalent to a prothrombin time between 19 and 22.5 seconds.

The widespread use of the INR will allow a direct comparison of results from different clinical laboratories, but it will undoubtedly take time for clinicians to become familiar with INR units, particularly the fact that for any change in a patient's coagulation status, the INR will change more than the prothrombin time. For example, if the ISI of a thromboplastin reagent is 2.4, an increase in the prothrombin time from 18 to 24 seconds more than doubles the INR value, which rises from 2.6 to 5.2. Although using the INR will require some adjustment, it is certainly a step in the right direction of achieving better control of anticoagulation therapy.

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Medical Treatment of Breast Cancer

THE MANAGEMENT OF carcinoma of the breast has been under intense review for the past decade and has been the source of several well-constructed, multi-institutional clinical trials. As data from these trials have matured, they have changed the practice of cancer management.

Recently eight-year follow-up data have been presented

on the recurrence patterns and survival rates of breast cancer patients randomly assigned to lumpectomy alone, lumpectomy with local x-ray therapy, or total mastectomy. For the three treatment groups there were no differences in overall survival or patterns of distant metastatic disease. Disease-free survival rates, excluding patients receiving lumpectomy in whom local x-ray treatment failed, also did not differ. These data offer the longest follow-up for a prospective study and provide an increasingly firm base for using less extensive surgical intervention in the primary management of breast cancer. In other published studies, the systemic use of chemotherapy or tamoxifen in patients with breast cancer without malignant nodes was shown to offer a survival advantage.

These trials in toto document the current trend of less extensive primary surgical therapy for breast cancer but with the use of systemic therapy beginning just after surgical treatment for most, if not all, patients. The data supporting the use of systemic adjuvant therapy for both patients with and without nodes showing malignant tumor must, however, be interpreted conservatively and with due attention to patient and clinical staging characteristics of those populations being reported.

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The Use of CPAP to Eliminate Obstructive Sleep Apnea

CONTINUOUS POSITIVE airway pressure (CPAP) applied through the nares is now the preferred treatment of clinically significant obstructive sleep apnea. Patients who use CPAP wear a mask that surrounds the nose and is secured by straps that fit around a patient's head. A long hollow tube is connected to a flow generator that initiates air flow at levels defined by a sleep study evaluation.

Continuous positive airway pressure is used to treat obstructive sleep apnea, which is characterized by an upper airway obstruction that impedes ventilation during sleep. Apnea is defined as the cessation of breathing of at least ten seconds' duration and may be caused by the collapse of redundant tissues in the upper airway, which is common in obese patients. In the absence of air flow, arterial oxygen levels fall and may be accompanied by a brain arousal or awakening—a two- to three-second electroencephalographic (EEG) disturbance. The large number of EEG arousals seen in these patients probably leads to the excessive daytime sleepiness that they have.

Nasal CPAP was first described in 1981 and gained pervasive acceptance in the sleep disorders community by 1986. Before CPAP, an upper airway operation, uvulopalatopharyngoplasty (UPPP), was the preferred therapy for patients with relatively severe sleep apnea. Unfortunately, UPPP has proved to be of limited success as only 45% of the patients had improved apnea indexes. Furthermore, patients with UPPP without tracheostomy did not fare better than control subjects when tested over a seven- to eight-year time frame after the operation. Nasal CPAP was revolutionary because it was less invasive and, when patients used it nightly, more effective than the operation. Patients using CPAP had no obstructive sleep apnea and a 100% survival rate over a seven- to eight-year period after the operation.

It is thought that nasal CPAP eliminates both snoring and obstructive sleep apnea by creating a pneumatic splint in the airway so that the airway remains patent during sleep. When nasal CPAP is applied at the appropriate levels—5 cm to 20 cm of water—arterial oxygen saturation levels improve and fewer EEG sleep arousals are noted. Within a short time—one day in some cases—patients may show a dramatic lessening of the severity of daytime sleepiness. The long-term use of CPAP is required unless the patient can lose enough weight to reverse the obstructive sleep apnea.

Patients who have an apnea index (number of apneas per hour of total sleep time) above 20 in our experience are the most tolerant of CPAP. Estimates from studies conducted at various centers around the world indicate that CPAP is well tolerated. Tolerance estimates range between 60% and 80% and are thought to be increased with close follow-up. Intolerance to CPAP is usually caused by nasal congestion, claustrophobia, or excessive CPAP pressure levels.

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New Dietary Concepts in Hypercholesterolemia

HYPERCHOLESTEROLEMIA increases the risk for coronary artery disease. This risk rises progressively with increasing cholesterol levels, especially with levels above 5.20 mmol per liter (200 mg per dl). More than half of adult North Americans have cholesterol levels in excess of 5.20 mmol per liter. Lowering serum cholesterol levels will reduce the incidence of coronary artery disease. Dietary modification to lower the consumption of cholesterol and total and saturated fats remains the mainstay of therapy.

Additional dietary concepts have recently become popular. One is the use of water-soluble fibers, found in oat bran, beans, and fruit pectin, to reduce total and low-density-lipoprotein (LDL) cholesterol levels. Eating oat bran, an inexpensive, palatable fiber, can lower total cholesterol levels by 3% to 26%; LDL cholesterol levels also decrease, but high-density-lipoprotein (HDL) cholesterol and triglyceride values usually remain unchanged. Most studies are short-term (3 to 12 weeks), but one showed persistent benefit to 99 weeks. Another soluble fiber, psyllium, used to regulate bowel function, also lowers total and LDL cholesterol levels. The long-term effects of soluble fibers on the incidence of coronary artery disease are unknown.

Soluble fibers are thought to lower serum cholesterol levels by binding bile salts in the intestine. In response, the liver increases its conversion of cholesterol to bile acids. The depletion of the liver cholesterol content stimulates a synthesis of LDL receptors, a primary mechanism for removing LDL cholesterol from serum. The addition of soluble fibers such as oat bran to a low-fat, low-cholesterol diet may be an inexpensive nonpharmacologic way to help reduce serum cholesterol levels.

Another dietary theory proposes that the type of fat ingested may play a more important role in determining serum cholesterol levels than the amount. People in Mediterranean countries who eat a diet high in total, predominantly monounsaturated fat have a low incidence of coronary artery disease. Short-term studies have compared the effects on serum lipids of volunteers who ingested diets high in total and monounsaturated fat, high in total and saturated fat, or low in total fat. The high-monounsaturated-fat and low-fat diets had similar effects in lowering total and LDL cholesterol levels when compared with the high-saturated-fat diet. These study diets differed from Mediterranean diets. They used liquid formulas low in complex carbohydrates, high in glucose, and high in safflower oils rather than olive oil. The long-term effects on serum lipids of diets high in total and monounsaturated fat have not been studied. It is premature to conclude that such a diet will lower the incidence of coronary artery disease. The current recommendations for North American adults include a small increase in monounsaturated fat consumption to partially replace decreased saturated fat intake.

What about fish oils, the ω-3 fatty acids? Pharmaceutical sales of fish oil capsules have dramatically increased. Interest developed when it was noted that coastal Eskimos and other populations whose diets are rich in these substances have a low incidence of coronary artery disease. Even in large quantities, ω-3 fatty acids cause only a modest decrease in serum cholesterol levels; they primarily lower triglyceride levels. They also decrease platelet aggregation and the synthesis of thromboxane A_2, factors implicated in the pathogenesis of atherosclerosis.

Whether ingesting ω-3 fatty acids will reduce the incidence of coronary artery disease is unknown. Patients should be informed that the typical North American diet, high in saturated fat, cannot be turned into an "Eskimo diet" by adding fish oil capsules. Eskimos have a high incidence of stroke, and there is concern this may be related to the hemostatic alterations of ω-3 fatty acids. To match the Eskimo diet in ω-3 fatty acids would require using as many as 30 to 60 capsules per day, with an average daily cost of $10. The use of fish oil capsules is not recommended. Epidemiologic evidence suggests that the frequent consumption of fish, whether high or low in ω-3 fatty acids, is associated with a decreased risk of coronary artery disease. Fish can provide a useful substitute for meat high in saturated fat.

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Recent Advances in Diagnosis and Treatment of Acute Pancreatitis

ACUTE PANCREATITIS is a commonly encountered clinical disorder. In the United States, alcohol abuse and biliary tract disease account for the vast majority of cases. Morbidity and death related to pancreatitis are largely confined to patients with severe necrotizing disease, which accounts for 10% to 18% of cases.

The diagnosis of pancreatitis is made clinically because histologic examination of the gland is not readily available. The clinical diagnosis may be supplemented or supported by laboratory or radiographic evidence. Efforts to improve either the sensitivity or specificity of the diagnosis with specific enzyme or isoenzyme measurements have been largely unsuccessful.

Although diagnostic imaging of the gland may be confirmatory, both ultrasonograms and computed tomograms may be normal in as many as 15% to 20% of patients with acute pancreatitis. The most useful role of computed tomography is in its ability to provide prognostic information and identify complications—abscess or pseudocyst—of pancreatitis. The use of magnetic resonance imaging in acute pancreatitis remains a research tool. Its poor spatial resolution makes it unreliable in differentiating inflammation from necrosis and other pancreatic abnormalities.

The treatment of acute pancreatitis is primarily supportive because most cases are of mild or moderate severity and have a universally good prognosis. Such patients need only be supported with fluid resuscitation and adequate analgesia. Nasogastric suction, H_2-receptor blockers, atropine, glucagon, aprotinin, and antibiotics have all proved ineffective in improving the outcome in patients with mild to moderate disease, and their use is not recommended.

Early morbidity and death in pancreatitis are related to cardiopulmonary collapse and renal failure, which occur in patients with severe necrotizing or hemorrhagic pancreatitis. Although clinical trials of the use of peritoneal lavage have failed to show an improvement in mortality, lavage may offer a means of support for those with cardiovascular collapse.

Although early death may not be avoided, late mortality may be prevented. Death after 10 to 14 days occurs as the result of septic complications. Controlled trials have shown that the prophylactic use of antibiotics is of no benefit in improving outcome, but these studies are flawed in that the population studied was at low risk (nonsevere pancreatitis). A growing body of literature suggests that bacterial contamination occurs more frequently—in 40% of cases—and earlier (seven to ten days) than previously assumed in patients with severe necrotizing pancreatitis. In this population, antibiotic prophylaxis may be beneficial.

Unfortunately, a case of sterile necrosis cannot be clinically differentiated from a case of infected necrosis. In both, patients may have fever, leukocytosis, and a clinically deteriorating course. Computed tomography-guided aspiration of necrotic areas or liquid collections has proved to be a reliable means of detecting or excluding bacterial infection. The presence of organisms on a Gram's stain or a culture requires either aggressive surgical debridement or radiologic catheter drainage.

Using an aggressive aspiration approach in patients with

severe necrotizing pancreatitis and early operative or catheter drainage may result in improved survival rates. The use of prophylactic antibiotics in these patients should be evaluated by a controlled trial.

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Misoprostol Therapy for Patients Taking Nonsteroidal Anti-inflammatory Drugs

GASTROPATHY INDUCED BY the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a major complication of these widely prescribed drugs. Patients at highest risk for gastropathy are those on long-term NSAID therapy, including the elderly, arthritic patients, and those with a history of abdominal pain or gastric intolerance to NSAIDs. The spectrum of gastropathy includes mucosal hemorrhages or erosions, gastric ulcer—present in as many as 15% of the population at risk—and duodenal ulcer, and any of these may present with complications such as gastrointestinal bleeding or perforation. Attempts to prevent NSAID-related gastropathy with H_2-receptor blockers and sucralfate have been unsuccessful, though these agents remain useful for healing established ulcers once NSAID therapy is discontinued.

The mechanism of NSAID-induced mucosal damage is not completely understood. The suppression of mucosal prostaglandin production and a reduction of mucosal blood flow by NSAIDs are contributing factors, and the presence of gastric acid is required. Prostaglandins such as misoprostol, a synthetic prostaglandin E_2 analogue, have been investigated for their role in gastric mucosal protection, particularly against insults such as from taking NSAIDs. In low doses these agents have cytoprotective properties such as enhancing mucosal blood flow and gastric mucous production. In higher doses they can inhibit gastric acid secretion. In healthy subjects misoprostol use has been shown to prevent mucosal lesions induced by NSAIDs and aspirin. Even with doses below antisecretory levels, patients had lowered endoscopic scores of mucosal damage, suggesting cytoprotection by misoprostol. Notably, abdominal pain and other gastrointestinal symptoms were not reduced in these short-term studies.

Two recent trials show the clinical usefulness of misoprostol in arthritic patients on NSAID therapy. One trial enrolled patients with abdominal pain but without gastric ulcers on endoscopy and showed a significantly reduced incidence of gastric ulcer in the group treated with misoprostol. Because the overall incidence of gastric ulcer was high, the study was terminated for ethical reasons before statistically significant data could be collected on the effects on duodenal ulcers. In a second study, misoprostol therapy produced substantial regression of gastropathy in patients with rheumatoid arthritis who continued on aspirin therapy. No exacerbation of arthritic symptoms was noted in patients treated with misoprostol.

Unfortunately, none of these studies have shown any consistent benefit on abdominal symptoms; in fact, some have shown worsened gastrointestinal symptoms in the misoprostol-treated patients. This is due in part to the side effects of the drug, which include diarrhea, dyspepsia, and abdominal pain, and may require reducing the dose from the recommended starting dose of 200 μg four times a day to 100 μg. Misoprostol also has uterotonic effects and may cause cramping, bleeding, or spontaneous abortion, necessitating extreme caution in prescribing to women of childbearing age and contraindicating its use in pregnancy.

Misoprostol therapy should certainly be considered for patients with disabling arthritis who need to continue on NSAID therapy despite a serious complication—such as gastric ulcer or gastrointestinal bleeding—from these agents. It may be indicated in symptomatic patients on NSAID therapy, particularly elderly or chronically ill persons, to prevent the development of gastric complications. Because its efficacy in reducing symptoms has not been shown, assessing any clinical benefit over the short term may be difficult, especially because many of these patients will not be followed up with endoscopy. The role of misoprostol therapy in high-risk asymptomatic patients without documented gastrointestinal complications bears further investigation. Its effects on the prevention and healing of duodenal ulcers need to be assessed. Finally, long-term studies are needed to evaluate the efficacy of misoprostol therapy in preventing more serious complications such as gastrointestinal bleeding and perforation and to identify the patient groups that may benefit from such therapy.

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Rheumatoid Arthritis and Methotrexate—A Renewed Partnership

METHOTREXATE was first used to treat hematologic malignant disorders in the late 1940s. It was later tried in rheumatic diseases with the assumption that the two groups of patients shared a similar pathophysiology. Because of the serious side effects associated with the earlier dosage regimens and the recognition of the dramatic effects of corticosteroids, its use was soon discarded. The modern application of methotrexate began in the 1960s when introduced in the treatment of psoriasis and dermatomyositis.

Since 1980 when an eight-year experience with the use of methotrexate to treat rheumatoid arthritis was described, several authors have published data supporting the relative safety and efficacy of its use in patients with this disorder. In 1988 the American College of Physicians published a "position paper" describing its use, and this year, after 45 years on the market, the Food and Drug Administration approved its use for the treatment of rheumatoid arthritis.

Methotrexate is a folic acid analogue. It inactivates intracellular enzymes, depleting the cell of reduced folates necessary for the formation of purines and pyrimidines and thus DNA. Its mechanism of action in rheumatoid arthritis is un-

known but would appear to include antirheumatic and anti-inflammatory properties. Specific actions described include the suppression of neutrophil chemotaxis and the enhancement of the function of killer cells. Administering leucovorin calcium can reverse clinical improvement, suggesting folate antagonism as a mechanism. No effect on prostaglandins has been reported.

The use of methotrexate should be considered when more traditional methods of treating rheumatoid arthritis, such as gold therapy, have failed. Although the accumulated data suggest that methotrexate as primary therapy may be recommended in the future, long-term follow-up information is not yet available to support the safety of this approach. Moreover, methotrexate has not yet been proved to induce true remissions in these patients. Severe flares of rheumatoid arthritis after discontinuing therapy have been reported.

Because of the potentially severe side effects, candidates for therapy must be selected carefully and monitored continuously. Contraindications include the presence of infection, hepatic disease, alcohol intake, or reduced renal function as estimated by an age-adjusted creatinine clearance. Relative contraindications include either hematologic abnormalities unrelated to rheumatoid arthritis or interstitial lung disease.

The baseline evaluation should include a complete blood count, blood chemistry values, a urinalysis, and a chest roentgenogram in all patients. Regularly scheduled monthly visits with a physician familiar with the drug and a redetermination of blood count and liver function indexes are prudent. The necessity of doing a liver biopsy is controversial, but most reports suggest a biopsy after a cumulative dose of 1,500 mg. Current practice based on accumulated experience is to do a biopsy only if liver enzyme levels remain elevated after stopping the drug. When evaluating a biopsy specimen, the awareness that pretreatment histologic abnormalities have been reported should be kept in mind. Pulmonary function should be assessed if respiratory symptoms develop because methotrexate toxic effects include interstitial pneumonitis. The initial dose is 7.5 mg one day per week with the maximal dose seldom exceeding 15 mg.

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Thrombolytic Therapy for Acute Myocardial Infarction

ADMINISTERING thrombolytic drugs to patients with acute myocardial infarction results in clot lysis and reperfusion of the occluded coronary artery in about 35% to 75% of patients. Successful reperfusion results in enhanced survival and improved left ventricular function, most likely owing to a decrease in infarct size. Furthermore, a reperfused infarct is less likely to undergo remodeling and expansion, resulting in less deterioration of left ventricular function in the days and weeks after infarction. Most trials have shown that initiating thrombolytic therapy early—within three hours after chest pain begins—improves the success of thrombolysis and survival compared with the results of giving thrombolytic therapy relatively late after the onset of chest pain. The Second International Study of Infarct Survival (ISIS-2) trial, however, showed that intravenous streptokinase therapy lengthened survival, even when given 12 to 24 hours after the start of symptoms. This may have been due to the presence of collateral circulation in certain patients, possibly delaying the time after which irreversible myocardial injury occurred. Alternatively, this may indicate that later reperfusion after a completed infarction may be of benefit by preventing infarct expansion. Many of the initial thrombolytic trials emphasized that the major improvement in survival occurred in patients with anterior myocardial infarctions. A trial from New Zealand, however, and the ISIS-2 trial showed that thrombolytic therapy improved survival rates in patients with inferior myocardial infarctions as well.

The possible benefits of coronary reperfusion in patients with acute myocardial infarctions need to be weighed against the side effects of thrombolytic therapy. The most serious side effect of thrombolytic therapy is intracranial bleeding, which occurs in about 0.5% of patients. Other side effects include bleeding from other sites, hypotension, and reperfusion arrhythmias. Streptokinase also has the potential to cause allergic reactions and, rarely, anaphylaxis. Risk factors that would preclude a patient from receiving thrombolytic therapy include the presence of active internal bleeding, a history of a previous cerebrovascular accident, neurosurgical procedure or head trauma, an intracranial neoplasm, an atrioventricular malformation or aneurysm, and a known bleeding disorder. Investigators have excluded patients older than 75 years from receiving thrombolytic therapy because of a perceived increased risk for intracranial bleeding. The ISIS-2 trial, however, showed no increased risk for intracranial bleeding following intravenous streptokinase therapy in patients older than 75 years. Further studies will be necessary to confirm this observation.

Because thrombolytic therapy fails to lyse coronary thrombi in about 25% of patients, coupled with the observed and perceived risks of coronary reocclusion and reinfarction, many investigators have examined the possible role of adjuvant pharmacologic therapy and mechanical reperfusion in patients receiving thrombolytic therapy. The ISIS-2 trial showed that using aspirin reduced mortality by 21% in patients with suspected myocardial infarctions. This reduced mortality was additive to that due to intravenous streptokinase therapy. Aspirin use also decreased the incidence of reinfarction in patients receiving intravenous streptokinase by approximately 50%. The Thrombolysis in Myocardial Infarction (TIMI) phase IIB trial found that the early administration of metoprolol reduced the incidence of recurrent angina compared with late metoprolol administration, starting on day 6 after an infarction. Furthermore, when given within two hours of the beginning of chest pain, metoprolol therapy reduced the combined incidence of nonfatal reinfarction and mortality. In patients with persistent coronary artery stenosis, coronary angioplasty done immediately after thrombolytic therapy results in increased complications and mortality compared with delayed angioplasty—that is, done one to seven days after an infarction. Furthermore, the TIMI phase IIB trial showed that doing angioplasty one to two days postinfarction failed to improve survival or left ventricular function or to reduce the incidence of reinfarction compared

with conservative management in these patients. Thus, it appears that most patients receiving thrombolytic therapy can be successfully managed without the need for routine coronary angioplasty unless they have symptoms or objective evidence of recurrent ischemia.

At this time there are no definitive data that would show the superiority of one thrombolytic agent over another in terms of improving survival or left ventricular function in patients with acute myocardial infarction. Although the TIMI phase I trial showed that, compared with streptokinase therapy, administering intravenous tissue plasminogen activator achieved a higher incidence of coronary artery patency 90 minutes after it was started, a New Zealand trial failed to show that giving tissue plasminogen activator was better than administering streptokinase in improving overall left ventricular function. It should be noted that both of these trials involved relatively small numbers of patients. Currently there are several large ongoing studies comparing the relative benefit of various thrombolytic agents on survival.

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Reducing Morbidity and Mortality Due to Asthma

DESPITE MAJOR ADVANCES in the understanding of its pathogenesis and the availability of a large number of drugs, morbidity and mortality due to asthma appear to be on the rise. Although the reasons for this disturbing paradox are unclear, there are certain broad treatment guidelines that, if diligently followed, will help to reduce the growing menace of asthma.

Although patients of any age, sex, and race can die of asthma, the disease more frequently ravages socioeconomically handicapped members of the society. In the United States blacks have a higher incidence of death from asthma than whites. Adults older than 65 years and children between the ages of 10 and 14 years are particularly susceptible. Persons with specific immunoglobulin E antibodies to common inhalant allergens are at an increased risk for acute severe attacks of asthma. Most of the patients who die of asthma have a history of severe, poorly controlled disease with poor compliance. Many of these patients also have emotional ailments, particularly depression, isolation, and problems of self-image.

Physicians often fail to realize that there is generally a poor correlation between the symptoms of asthma and the degree of airway obstruction. Patients, on the other hand, commonly develop a tolerance to their symptoms. Thus, there is a failure on the part of both physician and patient to appreciate the severity of bronchial narrowing. Educating patients about recognizing important symptoms and emphasizing the necessity of monitoring airway obstruction by peak flow measurements are the basic steps towards controlling asthma. More often than not, patients can be persuaded to buy a flow meter. Physicians who take care of asthma patients should not only have a peak flow meter on their desk but should also have easy access to a pulmonary function laboratory.

One of the problems related to asthma therapy lies in the way the treatment is delivered to the airways. Although the inhaled route is an effective way of delivering bronchodilators, surveys have shown that more than 50% of patients prescribed an aerosol inhaler used it incorrectly. Furthermore, other studies have revealed that physicians often do a less than satisfactory job of instructing their patients on how to use inhalers. The problem of poor coordination can now be corrected by using spacers and newly developed breath-actuated inhalers. These devices are of particular help in very young and elderly patients who find it hard to use metered-dose inhalers.

Although the treatment of asthma should be tailored to the needs of individual patients, inhaled selective β_2-adrenergic agents constitute the first line of therapy in chronic asthma. When a properly administered β_2-adrenergic drug—including the use of spacers and breath-actuated inhalers—does not provide effective relief of bronchospasm, aerosolized corticosteroids should be prescribed to suppress the airway inflammation that appears to underlie the severe bronchial hyperreactivity of asthma. If used effectively, this combination not only produces maximum improvement in peak flow rates but also cuts down the need for parenteral steroids. Patients who do not respond to the β_2-adrenergic drugs and aerosolized corticosteroids combination deserve a trial of cromolyn sodium. This prophylactic agent is particularly useful for young patients with asthma who are known to have allergies and exercise-induced asthma. Recent studies have found that cromolyn sodium reduces bronchial hyperreactivity in adult patients with asthma as well.

In summary, the rising tide of morbidity and death in asthma can be countered by recognizing high-risk patients, by accurately assessing the severity of airway obstruction, by properly delivering bronchodilators in the airway, and by prescribing cromolyn sodium and corticosteroids judiciously.

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Treatment of Small-Cell Lung Cancer

MANY COMBINATION chemotherapy regimens have activity in patients with small-cell lung cancer. In contrast to the treatment of non-small-cell lung cancer, surgical excision is not generally recommended for patients with small-cell lung cancer because of the propensity for distant spread of the

disease—even if it is not apparent on the initial clinical evaluation—and the excellent initial response to chemotherapy. Patients with both limited stage (disease present only in one side of the thorax and regional lymph nodes) and extensive stage (disease spread beyond the confines of limited disease) small-cell lung cancer have an excellent chance of responding to chemotherapy. Using standard regimens patients with limited disease have a 50% complete remission rate, and approximately 20% of patients with extensive disease will attain a complete remission. A complete remission implies total resolution of all clinical signs and symptoms and radiographic evidence of malignancy. Patients with small-cell lung cancer who achieve a complete remission have an improved quality of life and median survival. Unfortunately, recurrences frequently develop, and the median survivals for patients with limited disease and those with extensive disease are only 12 and 8 months, respectively.

The two most common combination chemotherapy regimens used in the United States for patients with small-cell lung cancer are vincristine sulfate, doxorubicin (Adriamycin) hydrochloride, and cyclophosphamide (VAC) and etoposide and cisplatin. In the past two years, four prospectively randomized clinical trials that tested combinations of these drugs alone and in conjunction with consolidative chest radiotherapy have been reported.

In 1987 the Cancer and Leukemia Group B reported the experience in 399 patients with limited disease who were randomly assigned to receive initial chemotherapy—vincristine, Adriamycin, cyclophosphamide, and etoposide—combined with chest radiotherapy versus delayed chest radiotherapy sandwiched between cycles of chemotherapy versus chemotherapy only. The complete remission rate and median survival were best in the group receiving combined methods. For initial chemotherapy combined with chest radiotherapy, the complete remission rate was 49% and median survival 13.4 months; for chemotherapy plus delayed radiotherapy, the complete remission rate was 58% and median survival 12.0 months; and for chemotherapy alone, the complete remission rate was 36% and the median survival 10.5 months. Disease-free survival was prolonged three to four months for the combined treatment methods.

Two studies were reported from the National Cancer Institute of Canada. In the first, 289 patients with extensive disease were randomly assigned to receive six cycles of VAC or six total cycles of VAC alternating each cycle with etoposide and cisplatin. Patients treated with the alternating regimen had a slightly increased complete remission rate (13% versus 10%) and prolonged median survival (9.6 months versus 8 months). No significant difference in overall survival was detected ($P=.4$).

The second study from the National Cancer Institute of Canada was undertaken in 300 patients with limited disease. Patients were randomly assigned to receive VAC alternating with etoposide and cisplatin for a total of six cycles, or three cycles of VAC followed by three cycles of etoposide and cisplatin. Again, the alternating regimen resulted in a slight but not significantly different increase in complete remission rate (52% versus 44%) and median survival (15.4 months versus 14.9 months).

In 1988 the Southeastern Cancer Study Group reported the experience in 148 patients with limited disease who were randomly assigned to receive six cycles of VAC or six cycles of VAC followed by two cycles of etoposide and cisplatin as consolidation therapy. Only responding patients were given consolidation therapy. The complete remission rates were similar in both groups (64% versus 65%), but the patients who received consolidation therapy had a significantly prolonged median survival (24.4 months versus 17 months, $P=.0094$).

In summary, a regimen of VAC alternating with etoposide and cisplatin was associated with a slight improvement in the complete remission rate and median survival, but the differences were generally small and of minimal clinical significance.

With current therapies, most patients with small-cell lung cancer continue to die of recurrent drug-resistant disease. Active basic and clinical research is underway to evaluate the mechanisms and means of reversing drug resistance in these patients. Because the chance of cure using any standard treatment method is extremely small, all eligible patients with this disease should continue to be enrolled in appropriately designed clinical trials.

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Editorials

Cirrhosis, Alcohol, and the Heart

ELSEWHERE IN THIS JOURNAL, Lee has presented an excellent comprehensive summary of the cardiac and circulatory abnormalities often seen accompanying liver cirrhosis. For the most part, these reflect damage to the heart and liver from chronic alcohol abuse, although nonalcoholic cirrhosis can produce subtle changes in cardiac performance as well.

Clinically a patient with alcoholic cirrhosis, particularly in a decompensated state, frequently shows signs suggesting a hyperkinetic circulation. Among these are an obvious increase in the oxygen saturation of antecubital vein blood compared with that seen in the usual patient, with palmar erythema, warm hands, the occasional presence of clubbed fingers, and bounding peripheral pulses. Repeated studies, as noted in Lee's review, have documented the presence of a high cardiac output in these patients that is unrelated to thiamine deficiency, anemia, or an increase in the circulating blood volume. The arterial blood pressure is usually normal or even low, indicating that systemic vascular resistance is reduced. A number of theories have been proposed to account for the generalized systemic vasodilation that is observed, but the exact mechanism remains a matter of speculation.

This chronic decrease in afterload appears to outweigh the frequent presence of some degree of depressed myocardial contractility in patients suffering from alcoholic cirrhosis. As a result, there occurs the paradox of a patient with impaired myocardial function having an increased stroke output. It is of interest that some of these patients when studied serially over days to months while hepatic compensation was being restored, and after prolonged abstinence from alcohol, show a return of their cardiac output to the normal range.[1]

Clinicians at times assume that high-output heart failure occurs in decompensated cirrhosis not only because a hyperkinetic circulatory state is evident, but also because marked peripheral edema, ascites, and pleural effusions are present. Heart failure may be erroneously assumed because the central venous pressure is elevated and, therefore, there appears to be an increase in the right ventricular filling pressure. The rise in central venous pressure, however, is inevitably modest and primarily reflects transmission of the increase in mean intrapleural pressure resulting from tense ascites with a resultant elevation of the diaphragm. This can be readily demonstrated by the immediate fall in right atrial and central venous pressures that will occur with abdominal paracentesis sufficient to lower significantly the intra-abdominal pressure.[1] Furthermore, these patients do not have gross cardiomegaly, S_3 gallops, pulsus alternans, or other findings suggesting cardiac failure. This view is further supported by an echocardiographic examination, which usually reveals a normal or minimally increased left ventricular volume and a normal global ejection fraction.

In his review, Lee has suggested that tense ascites, which increases the intrathoracic and intrapleural pressures, decreases the cardiac transmural filling pressure. However, the modest increase in right atrial and central venous pressures, seen when a catheter is placed in these sites in a cirrhotic patient with tense ascites, suggests that the increase in the intravascularly measured pressure is reflecting an approximately corresponding increment in intrathoracic pressure. I am unaware of any direct measurement of transmural filling pressure in patients with cirrhosis; it would require the simultaneous measurement of end-diastolic ventricular pressure and intrapericardial pressure at the same hydrostatic level. The immediate rise in cardiac output after paracentesis is not in itself evidence of improved myocardial contractility. Instead, it may reflect improved venous return to the heart following a reduction of the intra-abdominal pressure. This might be associated with an actual increase in the transmural filling pressure despite the fall in measured venous or right atrial pressure if the intrapleural (and, therefore, intrapericardial) pressure actually falls more. Furthermore, the increase in cardiac output may result from a fall in the afterload as well, reflecting a drop in the intra-abdominal pressure. In any case, it is hard to make a strong argument for the view that tense ascites per se directly impairs cardiac performance.

It is intriguing that alcoholic cardiomyopathy with classic overt low-output congestive heart failure is seldom seen in patients with cirrhosis. Lee has pointed out two principal explanations for this observation, namely the masking of overt failure by a chronic unloading of the left ventricle because of the low peripheral resistance and the statistical fact that two diseases, each of which may result in premature death, will correlate negatively at autopsy. There is, however, a third possible explanation that deserves comment. Alcoholic dilated congestive cardiomyopathy generally develops after many years of heavy alcohol consumption regardless of the presence of an otherwise good nutritional status. Presumably, however, good overall nutrition is protective to the liver, preventing or at least delaying the development of cirrhosis. In other words, patients with chronic, severe alcoholism will eventually have either alcoholic cirrhosis or alcoholic cardiomyopathy, largely depending on their dietary habits. But even those in whom cirrhosis develops will usually exhibit impaired ventricular performance, that is, a latent or preclinical cardiomyopathy that can be shown when the heart is stressed with exercise or with pressors such as an angiotensin infusion. This is a reflection of myocardial damage resulting from chronic alcohol abuse, however, and is not due to cirrhosis per se.

The relationship between cirrhosis, alcohol consumption, and coronary atherosclerosis remains an enigma. Lee in his review points out that most autopsy studies reveal a lower prevalence of coronary atherosclerosis and myocardial infarction among cirrhotic patients than in controls. This is in agreement with our observations at San Francisco General Hospital where postmortem examinations on 105 patients with cirrhosis compared with 105 age- and sex-matched controls showed a lesser incidence and severity of coronary atherosclerosis.[1] It should be noted, however, that many of these autopsy studies have been criticized on the basis that the respective control groups had an excess of patients with hypertensive and atherosclerotic heart disease and were not truly representative of the populations to which the cirrhotic patients belonged.[2]

Many explanations have been put forth regarding the apparent negative association between cirrhosis and coronary

atherosclerosis. These include the statistical bias of studying at necropsy two potentially lethal diseases; the lowered blood pressure, increased fibrinolytic activity, and the hyperestrogenism found in cirrhotic patients; and the ability of alcohol consumption to increase high-density-lipoprotein (HDL) cholesterol levels significantly. The last is frequently cited to explain the many epidemiologic observations that show that moderate alcohol consumption itself, regardless of the presence or absence of cirrhosis, appears to be associated with a reduced mortality from coronary heart disease. That moderate alcohol consumption is protective against the development of coronary atherosclerosis is particularly intriguing in light of the known association between alcohol consumption and hypertension,[3] a known risk factor for coronary heart disease.

The protective effect of HDL cholesterol in the prevention of coronary heart disease appears to reside in a specific association with the HDL_2 subfraction.[4] Alcohol consumption, however, appears to preferentially affect the unprotective HDL_3 subfraction.[5] Further confounding this issue is the observation that the curve relating coronary heart disease mortality and alcohol use appears to be U-shaped. That is, there is substantial evidence to suggest that habitually heavy alcohol intake, in contrast to so-called moderate intake, actually results in an excess of coronary heart disease deaths.[6] The validity of this observation is supported by data showing an increase in the rate of nonfatal coronary heart disease as well in those who have a heavy alcohol consumption.[7]

It hardly makes sense today in light of the lack of understanding of the mechanisms by which moderate alcohol consumption may protect against atherogenesis to recommend its use for this purpose. Aside from the social issue of advocating the consumption of moderate amounts of a substance known to lead frequently to serious abuse, the relative risk reduction for coronary heart disease can be achieved more readily and appropriately by attention to directly eliminating the more serious risk factors such as cigarette smoking, hypertension, hypercholesterolemia, and obesity.

Alcohol abuse is the most common among the known causes of cardiomyopathy. Coronary heart disease is the leading cause of death in the industrialized world. Yet, it is clear from the above discussion that many questions remain unanswered concerning the mechanisms and association between alcohol consumption, cirrhosis, and both nonischemic and ischemic heart disease. What emerges is that despite a great number of studies in recent years involving alcohol both in animals and in humans, much further research is needed. In the interim, the one therapeutic recommendation that is readily apparent is that abstinence from alcohol is crucial to patients not only with overt cirrhosis or alcoholic cardiomyopathy, but to those who habitually ingest large amounts of alcohol even in the absence of clinical heart or liver disease.

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Perioperative Glucose Control in Diabetic Patients—Strategies for the 1990s

PERIOPERATIVE CONTROL of plasma glucose levels in diabetic patients is often a challenge. A number of factors combine to make management difficult. When patients are admitted for surgery, the physicians who will be managing their diabetes in the hospital may not have all the desirable information about the patients' treatment programs, recent levels of glucose control, existing complications, or comorbid conditions. The stress of a surgical procedure, postoperative pain, and inactivity usually causes a temporary increase in insulin requirements. Food intake is prohibited or unpredictable. Glucose is given intravenously at varying rates with maintenance fluids or medications. Even a diabetic patient on intensive management who has achieved normal or near-normal plasma glucose levels as an outpatient usually requires close attention and modification of treatment to deal with changing insulin requirements in the postoperative period.

Elsewhere in this issue, Gavin makes several important points that deserve clarification and emphasis. I will focus on two points that should have the greatest impact on the management of diabetes in patients having an operation in the 1990s: bedside blood glucose monitoring and intravenous insulin administration.

The desired range of metabolic control for preoperative diabetic patients is like a target with three rings. The outer ring of the target is the avoidance of both serious hypoglycemia and diabetic ketoacidosis. This can be accomplished in a variety of ways with little effort, keeping the plasma glucose level between approximately 2.8 and 22.2 mmol per liter (50 and 400 mg per dl). The second ring of the target is the broad range of plasma glucose—approximately 3.9 to 12.2 mmol per liter (70 to 220 mg per dl)—that is not associated with obvious signs or symptoms. To achieve this level of control requires a bit of effort but should be attainable in most patients and in most hospital settings. The bull's-eye of this target is normal or near-normal glucose levels—4.4 to 8.3 mmol per liter (80 to 150 mg per dl)—that may enhance wound healing and reduce the risk of infection by optimizing leukocyte function.

A major problem in convincing clinicians that meticulous control of plasma glucose levels is important for diabetic patients after an operation is that, other than missing the target altogether, neither clinicians nor patients are likely to ever appreciate the results of good control. Patients with poor glucose control often recover from an operation without obvious adverse effects. Patients with good glucose control (or even nondiabetics) may have poor wound healing or postoperative infection unrelated to their plasma glucose levels. Because there are so many variables, there will probably never be a definitive study that clearly shows the benefits of good glucose control for a diabetic patient after surgical treatment. There is sufficient circumstantial evidence, however, to warrant a goal of normal or near-normal glucose

levels in most if not all diabetic patients. This goal should be modified if attaining it is unsafe—the patient has serious hypoglycemia—or if the effort required to achieve it is greater than the potential benefits.

The most notable advance in diabetes management since the discovery of insulin has been the availability of methods that allow frequent blood glucose measurements with a rapid turnaround. The self-monitoring of blood glucose levels has permitted intensive therapy for ambulatory diabetic patients to achieve long-term normoglycemia to minimize the complications of diabetes. Self-testing of the blood glucose concentration is a prerequisite for tight glucose control. A number of glucose monitoring systems that provide satisfactory results are available. About ten years ago most diabetologists substituted patient self-monitoring of blood glucose levels for urine glucose testing in ambulatory patients. There is no question that bedside blood glucose monitoring can be useful in the hospital, allowing clinicians to detect trends and adjust treatment programs. Many hospitals have been slow to implement bedside blood glucose monitoring programs, however, for a variety of reasons that usually do not stand up to close examination. Bedside blood glucose testing should be instituted in all hospitals and should be available on most if not all hospital service areas, particularly where postoperative diabetic patients are cared for. The American Diabetes Association has provided guidelines, including training and quality control, that should be followed for the proper use of glucose meters in hospital.[1]

With the availability of techniques that permit more frequent monitoring of blood glucose concentrations came the realization that using the traditional approach of subcutaneously administering insulin to control blood glucose levels often hit only the outside ring of the glucose target. This led to the development of strategies for intravenous insulin administration. Insulin given intravenously has the advantage over subcutaneous insulin of allowing a more rapid responsiveness to changing insulin requirements. Not only can hyperglycemia be better controlled with intravenous insulin, but our experience shows that hypoglycemia is less common when insulin is given intravenously instead of subcutaneously.

About five years ago we began working on an algorithm for an "insulin drip" using simple adjustments in the insulin drip rate based on bedside blood glucose determinations every two hours.[2] Emory University Hospital had already instituted a program of bedside glucose monitoring. This approach, which works best with an infusion pump or a similar device to control the rate of insulin infusion, provides excellent glucose control in most patients postoperatively and is also useful for stabilizing poorly controlled patients before an operation. The algorithm is flexible and allows the insulin dose to be titrated for almost any circumstances. Although our algorithm is intended to work as an "automatic pilot," it includes provisions for physician notification if a patient's blood glucose level is not maintained in the target range. For patients undergoing a major operation who will require insulin coverage, we start the insulin drip on the morning of the surgical procedure if the patient has been in reasonable control or the night before if preoperative control has been poor or questionable. For most patients, preoperative control can be achieved and postoperative control can be maintained until the patient is ready to resume eating and go back on a regimen of subcutaneous insulin.

Our insulin drip system is simple and effective, and we have come to rely on it (or even take it for granted) in a variety of circumstances, such as for diabetic patients who have nausea and vomiting or are not taking fluids or solids by mouth for reasons other than surgery. There are, however, simpler strategies that can be used for administering insulin intravenously to stable diabetic patients where less rigid glucose control is acceptable. Simply adding a regular insulin injection to maintenance intravenous fluids with dextrose is likely to hit the second ring of the glucose target most of the time. For most patients, an insulin infusion rate of 1.0 to 2.0 units per hour is satisfactory. Of course, bedside blood glucose monitoring should be done every four to six hours and treatment modified as needed.

Some diabetic patients undergoing minor surgical procedures can be managed with subcutaneous insulin or no insulin at all. Type II diabetic patients who are well controlled with diet or oral hypoglycemic agents who are undergoing minor procedures and will be eating soon afterwards can be managed by avoiding glucose in their intravenous fluids and with blood glucose monitoring; subcutaneous or intravenous insulin can be added later if needed. Insulin-requiring patients whose diabetes is well controlled can be managed during a minor procedure that is scheduled early in the day by giving a fraction (⅓ to ½) of their usual insulin dose subcutaneously before surgery and a "sliding scale" of subcutaneous regular insulin injections every four to six hours afterwards as needed.

For optimal management of diabetic patients in hospital, bedside glucose monitoring should be available. Insulin treatment should be tailored to each patient. For minor procedures, insulin therapy can be withheld or given subcutaneously as a fraction of the usual dose. For major procedures in insulin-treated patients, intravenous insulin is preferred over subcutaneous insulin. A flexible insulin drip provides better glucose control than a fixed-rate insulin drip, but a simple, fixed-rate insulin drip—with insulin added to intravenous fluids with dextrose—can be used if infusion pumps or frequent blood glucose monitoring are not available. If possible, clinicians who have special interest and expertise should be called on to manage diabetic patients in the hospital for an operation or an intercurrent illness.[3] Whoever is called should be using these tools to achieve the best possible glucose control for their patients.

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Professional Values and Organized Medicine

THERE IS A GROWING CONCERN that organized medicine may not be attracting new members as well as it should, and this in spite of some intense efforts at recruitment by many medical associations. There is disturbing evidence that medical asso-

ciation membership growth overall is not keeping pace with the rapidly increasing number of physicians who are coming into practice. In fact, many of the associations that make up the American Medical Association (AMA) seem to be experiencing both an aging membership and problems attracting younger physicians, especially women.

It is difficult to be sure of the reasons for this, and many explanations have been offered. Among these, it is said that organized medicine does not present ready role models for young physicians in training. Specialty and subspecialty societies are more collegial to their interests than are the county, state, and national organizations that embrace all the specialties. Many, in and out of the profession, have begun to perceive organized medicine as a self-serving special interest group, and, indeed, the preservation of what they believe to be important in a changing practice environment does occupy much of the time and energy of the professional leadership of organized medicine, who in turn often feel that their efforts are unappreciated by physicians who have not joined their medical societies.

This brings up the question of professional values and whether these may be different among at least some physicians who are not members of organized medicine. For example, many academic physicians, who often serve as mentors and role models for young physicians, are more specialty-oriented and encourage their students and trainees to join their specialty and subspecialty societies, and this they do. But beyond this, there is reason to think that young physicians may be marching to a somewhat different drummer. Many seem to be more accepting of the changes that are occurring in medical practice, more willing to accept some security at the price of some freedom and to trade some income for fewer hassles, less paperwork, paid malpractice coverage, and more time with their families and for other professional or nonprofessional interests. Women physicians are rapidly increasing in number but have yet to find a comfortable home in organized medicine. And many young physicians now enter into practice with enough family and financial burdens that the dues structure of organized medicine may seem to them a large and relatively unrewarding expense. Taking all this in the aggregate, there may be a considerable and even growing mismatch between what organized medicine has to offer and the interests and values of many young physicians.

This deserves attention. To be sure, a very good case can be made that organized medicine and the AMA stand for much that is not self-serving for physicians and is very much in the public interest. There is an exemplary record of AMA contributions to better health for all Americans. Many perceive these ongoing activities of organized medicine now to have become secondary to a more primary concern with protecting physicians' fees and income. It may be that this perception of organized medicine as primarily a self-interest group is starting to do more harm than good, both with the public and in the political arena. Special interest groups in general are beginning to incur public criticism and disapproval, and this criticism of medicine as a special interest group is known to be shared by at least some physicians who might otherwise be members of organized medicine.

Things are not going too well with organized medicine and the medical profession. Not only are there membership recruitment problems, but powerful forces are arrayed against the profession and, it seems, even against needed health care. The profession itself is being fractionated from within and without, and its authority and clout are not nearly what they were not very long ago. Some battles are being won, but there is a growing sense that ground is being lost overall.

One wonders if it is not time for organized medicine to look for a new and quite different approach, perhaps to raise a different standard to which most if not all physicians could proudly repair, a standard that might begin to identify with some of the larger interests or professional values that are widely held among almost all physicians, a standard that would transcend specialty and even economic interests and make any physician feel good and even proud to be a member of the county, state, and national medical association. And where might such professional values be found? One might look to some of the reasons physicians enter into medicine in the first place. Most are or have been motivated by a desire to serve people who need help—that is, patients; to be part of a profession that is both challenging and truly needed; and then, to promote human health and well being in the larger society. It is hard to be a physician and not have or have had these interests. They must be widely shared.

If something like this were to be its more transcendent purpose and goal, organized medicine would need to begin to shift some of its priorities. Some genuine social and political power might result from doing so. Patients are becoming underdogs in patient care. No one really defends them. The public is hungry for impartial authority and integrity throughout health care. And health and illness in the workplace, the community, and in regional, national, and global environments cry out for disinterested, authoritative professional leadership. A physician might not just feel good, but even proud, to be part of a professional organization that at its local, state, or national level truly stood for and aggressively promoted the broader and widely shared values in health and health care that attracted physicians to the profession in the first place. There is much that could be done by medical associations were they to stand firmly and overtly in the patient and public interest. Where they stood and what they did would surely be understood and appreciated by the public and in the legislatures, where the real power in health care lies. Were this to be done, it could help in a big way to restore some missing clout and prestige to the profession.

MSMW

Case Reports

Aortic Valvulitis in a Patient With Wegener's Granulomatosis

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WEGENER'S GRANULOMATOSIS was characterized as a clinical syndrome by Wegener in 1936.[1] Manifested by granulomatous vasculitis of the upper and lower respiratory tracts and by glomerulonephritis, Wegener's granulomatosis is frequently associated with vasculitis involving other organs. Clinically evident cardiac disease is uncommon. In this report we describe the case of a patient with Wegener's granulomatosis who presented with acute aortic insufficiency requiring surgical replacement. The histologic examination of the native valve revealed changes consistent with Wegener's granulomatosis.

Report of a Case

The patient, a 77-year-old woman, was transferred to the University of California, San Francisco (UCSF), Medical Center in early November 1987 for worsening dyspnea, pulmonary infiltrates, and cavitary lesions of the lung. She had had a right upper lobectomy for removal of a solitary cavitary lesion in November 1986, which on pathologic examination was diagnosed as a lung abscess. The patient was well until early October 1987 when she noted dyspnea on exertion and a cough productive of blood-streaked mucus. She had a long history of sinus problems that had recently worsened with several episodes of bleeding from her left nostril. Her dyspnea became more severe, and paroxysmal nocturnal dyspnea and orthopnea developed. She had also recently noted a rash on her legs and hands. A chest x-ray film revealed bilateral infiltrates and cavitary lesions of the lung.

In late October on admission to another hospital, she had bibasilar rales in her lungs; no gallop or murmur was heard. She had petechiae and purpura on the dorsum of her feet and the periungual areas of her hands. Arterial blood gas determinations made while the patient was receiving six liters of oxygen by mask revealed a pH of 7.44, a partial carbon dioxide pressure of 32 mm of mercury, and a partial oxygen pressure of 65 mm of mercury. Fine needle aspiration of a cavitary lesion was reported to show caseous necrosis, and treatment with isoniazid and rifampin was begun for presumed tuberculosis. The patient's respiratory status continued to deteriorate, and she was transferred to UCSF for further evaluation.

On admission, the patient's blood pressure was 130/40 mm of mercury, her pulse was 120 per minute, and temperature 37°C (98.6°F). There were many raised purpura on the dorsum of her feet and several raised, firm, tender, pustular nodules on the periungual areas of her fingers. She had scleritis of her right eye. There was clinical evidence of congestive heart failure, including rales in the lower half of her lung fields, a jugular venous pressure of 10 cm of water, and a summation gallop with a grade II/VI systolic murmur at the base and a grade I/VI blowing diastolic murmur at the left sternal border. In addition, there was 4+ pitting pedal edema up to the knees.

Laboratory studies elicited the following values: hematocrit 0.28, leukocyte count 13.2×10^9 per liter, blood urea nitrogen 23.2 mmol per liter of urea (65 mg per dl [normal, 3.0 to 6.5 mmol per liter]), creatinine 132 μmol per liter (1.5 mg per dl [normal, 50 to 110 μmol per liter]), prothrombin time 13.4 seconds, albumin 26 grams per liter (2.6 grams per dl), C3 1 gram per liter (100 mg per dl), C4 0.24 grams per liter (23.8 mg per dl), and CH_{50} 0.034 U per liter (34.0 units per ml). A urinalysis showed 0.3 grams per liter protein by dipstick, 40 leukocytes per high-power field, and 10 erythrocytes per high-power field; no casts were seen. On a chest roentgenogram she had worsening diffuse hazy densities and cavitations bilaterally. An electrocardiogram showed sinus tachycardia, normal intervals, and nonspecific ST segment and T-wave abnormalities in the inferolateral leads.

Five sets of blood cultures were done, and all were negative for pathogens. Culture of specimens of pustular lesion on the hand and of sputum elicited no pathogens. Empiric antibiotic therapy was begun for presumed bacterial endocarditis. An echocardiogram showed severe aortic insufficiency with mild left ventricular dilatation. The left ventricular contractile function was moderately decreased. There was moderate mitral regurgitation and a suggestion of a small vegetation (less than 5 mm) on the posterior leaflet of the mitral valve.

The patient's congestive heart failure continued to worsen, and she was taken to the operating room on the second hospital day for a valve replacement. On gross inspection, the right and left coronary cusps of the aortic valve appeared normal but the noncoronary cusp was red and thickened. The anterior leaflet of the mitral valve was slightly thickened, and the posterior leaflet was normal. No vegetations were seen. The aortic valve was excised, and a Carpentier-Edwards porcine prosthesis was placed.

On pathologic examination, the aortic valve showed myxomatous change and degeneration of collagen consistent with collagen vascular disease (Figure 1). The inflammatory response was insignificant, and there was no evidence of bacterial endocarditis. Culture of a specimen of the aortic valve and a swab of the mitral valve was negative for bacteria. A review of a specimen of the pulmonary lesion removed in 1986 showed necrotizing granulomatous inflammation and arteritis consistent with Wegener's granulomatosis. A review of a skin biopsy specimen of a purpuric lesion on the patient's elbow a day before transfer showed vasculitis and extravascular granulomatous changes, also consistent with Wegener's granulomatosis.

Postoperatively the patient had renal insufficiency with a peak blood urea nitrogen level of 39.3 mmol per liter of urea

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(110 mg per dl) and a creatinine level of 371 μmol per liter (4.2 mg per dl). A urinalysis showed pyuria and hematuria. Following the diagnosis of Wegener's granulomatosis, she received an intravenous pulse dose of 800 mg cyclophosphamide, and a regimen of methylprednisolone sodium succinate, 60 mg a day, was begun. The patient's condition gradually improved, and she was discharged to a rehabilitation facility six weeks after admission on a regimen of cyclophosphamide, 75 mg per day, and prednisone, 60 mg per day, with considerable resolution of her pulmonary and skin lesions.

Comment

This case fulfills the clinicopathologic criteria for Wegener's granulomatosis described by Godman and Churg,[2] although the patient's clinical course was somewhat protracted.[3] The initial manifestation of her disease was a cavitary lung lesion that was removed and misinterpreted as a lung abscess. Even though immunosuppressive therapy was not given, nearly a year passed before she was seen again with extensive pulmonary, ocular, dermatologic, and aortic valve involvement. In addition, the renal failure that developed postoperatively was presumably due to glomerulonephritis, although no renal biopsy was done to confirm this.

Although Wegener's granulomatosis is a systemic disorder, clinical evidence of cardiac involvement is uncommon. Involvement of the heart has been reported in 30% of patients at autopsy.[4] In a recent report of 85 patients being observed for Wegener's granulomatosis at the National Institutes of Health, 12% had clinical evidence of cardiac involvement, usually of the pericardium and myocardium.[5] Involvement of the heart valves is rare and generally noted at autopsy.

We think this is the first reported case of pathologically documented involvement of the aortic valve in association with Wegener's granulomatosis. While myxomatous alteration of a valve is common and not always associated with underlying disease, degeneration of collagen representing early fibrinoid change is seen primarily in the collagen vascular diseases. Inflammation and fibrinoid necrosis of the mitral valve have been reported in six patients with Wegener's granulomatosis at autopsy.[2,6-9] Two cases of presumed aortic valve involvement in Wegener's granulomatosis have been reported. Gerbracht and co-workers reported the case of a 20-year-old man who suffered a myocardial infarction five days after immunosuppressive therapy was begun following an initial diagnosis of Wegener's granulomatosis.[10] An echocardiogram showed increased reflectance of the noncoronary cusp of the aortic valve, which returned to normal over two months with treatment. Dabbagh and associates reported the case of a 16-year-old boy in whom aortic insufficiency developed, detected by examination and echocardiogram during the third week of immunosuppression treatment of Wegener's granulomatosis.[11]

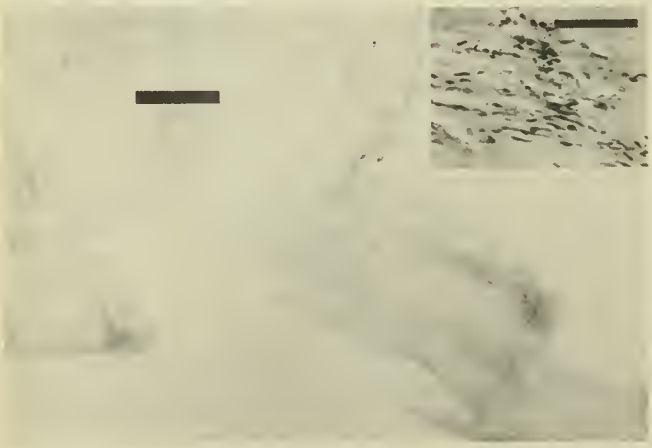

Figure 1.—On histologic examination, a specimen of the aortic valve shows myxomatous degeneration (hematoxylin and eosin; original magnification × 10, scale = 1 mm). **Inset,** There is focal necrosis of collagen (hematoxylin and eosin; original magnification × 100, scale = 0.1 mm).

In summary, although aortic valvular involvement in Wegener's granulomatosis is rare, this case shows that it does occur and may be severe enough to require emergent surgical intervention. The pathologic changes in the valve leaflets, while not specific, are unusual and suggest the presence of a collagen vascular disease.

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Intestinal Pseudo-obstruction Related to Using Verapamil

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VERAPAMIL has become increasingly popular for treating supraventricular tachycardia, angina pectoris, and hypertension.[1-3] Gastrointestinal adverse effects of using verapamil include constipation and nausea.[4] The constipation is frequently substantial enough to warrant discontinuing the medication and using an alternative. We report a case of intestinal pseudo-obstruction apparently aggravated by the use of verapamil for supraventricular tachycardia. This adverse effect appears to be a logical extension of the drug's action.

Report of a Case

The patient, a 73-year-old woman, was admitted to hospital in May 1988 because for two weeks she had had right

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lower abdominal pain, anorexia, and general malaise. She had no serious present or previous medical problems except for an appendectomy in her youth. She took no medications.

Examination on admission revealed a temperature of 37.6°C (99.6°F) and an 8- by 8-cm tender, fixed mass in the right lower quadrant of the abdomen. A pelvic and rectal examination showed no abnormalities. X-ray studies using a diatrizoate meglumine (Gastrografin) enema showed a partially obstructing mass lesion of the proximal right colon, consistent with a neoplasm. The patient was taken to surgery the day after admission where an adenocarcinoma of the ascending colon was seen, with a walled-off abscess within the tumor itself. There was no gross metastasis. A right hemicolectomy was done with an ileotransverse colostomy.

The patient was treated before and after the operation with the intravenous administration of cefotetan and of meperidine hydrochloride for incisional pain. Pulmonary atelectasis responded to pulmonary toilet. By the fourth postoperative day, she was passing flatus, and no further narcotics were required. Nasogastric suction was discontinued, and she began taking clear liquids. The following day, however, she had abdominal distension associated with emesis and diarrhea. Examination of a stool specimen did not show leukocytes, and a toxin screen was negative for *Clostridium difficile.* Nasogastric suction was reinstituted. The findings on abdominal x-ray films were consistent with an ileus.

On the eighth postoperative day, a regimen of total parenteral nutrition was begun because of persistent gastrointestinal malfunction and her deteriorating nutritional state. At this time, the patient had an asymptomatic supraventricular tachycardia at a rate of 160 beats per minute. This was successfully controlled with the intravenous administration of verapamil, with the subsequent addition of digitalis.

Abdominal distension and intermittent diarrhea persisted for the next week. Monitoring of electrolytes during this period showed no abnormalities except for a transient low magnesium level of 0.58 mmol per liter (1.4 mg per dl) that was corrected. An abdominal computed tomographic scan showed no evidence of abscess. A flexible sigmoidoscopy revealed no pseudomembranous colitis. Episodes of supraventricular tachycardia reappeared, and the patient was placed on a maintenance regimen of verapamil, 5 mg intravenously every eight hours, and digitalis. On this schedule the supraventricular arrhythmia resolved. Repeat plain x-ray films of the abdomen showed a pattern consistent with a small bowel obstruction, and a long Cantor tube was placed. Although this was initially successful, later attempts at feeding resulted in recurrent emesis and abdominal distension. On the 19th postoperative day, an exploratory laparotomy was done that showed several soft, nonobstructing adhesions. The ileotransverse colostomy anastomosis was normal, and no abscess was found. The small bowel was dilated with no mechanical obstruction.

The patient was continued on total parenteral nutrition and Cantor tube decompression after the second operation with an ileus persisting. By the third postoperative day, narcotic use was discontinued. Therapy with metoclopramide hydrochloride, 10 mg given intravenously every six hours, was started with no lessening of the ileus. On the sixth postoperative day, the verapamil therapy was discontinued to see if it could be adversely affecting the patient's intestinal motility. The next day, the patient had a return of normal bowel sounds with three bowel movements. Her abdominal distension rapidly resolved, and she was given solid food without difficulty. She was discharged from the hospital a few days later and has has no gastrointestinal complaints since.

Discussion

Through its action on the slow calcium channel, verapamil has substantial effects on cardiac electrophysiology,[5] vascular smooth muscle,[6] and gastrointestinal tract contractility.[7] In animals, verapamil has been shown to inhibit the pendular movement of rabbit ileum,[7] to antagonize the contractile response of rat duodenal muscle to calcium,[8] to inhibit gastrointestinal transit in mice,[9] and to potentiate opiate-induced inhibition of gastrointestinal transit in mice.[9]

Constipation is the most common adverse effect of verapamil use in humans.[10] The adverse incidence of constipation is usually reported to be in the range of 6% to 8% but can be as high as 42%.[4] While this may be more of a nuisance than a disability, in one instance fecal impaction related to verapamil use in an 80-year-old man has been reported.[11]

We are not aware of previous reports of intestinal pseudo-obstruction related to verapamil use, but anecdotal reports submitted to the manufacturer have included three cases of apparent paralytic ileus and two cases of bowel obstruction without mechanical obstruction. One of the patients had pneumonia, and others had had a recent operation (K. J. Rakowski, MD, Director, Corporate Safety Assurance, G D Searle & Company, oral communication, August 1988).

While the patient had gastrointestinal symptoms before using verapamil, we propose that its use contributed to the prolonged postoperative ileus and pseudo-obstruction. The patient had persistent difficulties that were not explainable on the basis of infection, narcotic usage, metabolic abnormalities, adhesive bands, or other mechanical disturbances. The use of metoclopramide did not produce a substantial improvement in the patient's clinical condition, nor did it obviate the second operation. Rather, when the verapamil use was discontinued, she had an impressively rapid and steady improvement in her condition. There was overnight initiation of flatus and bowel movements in a patient who had been having a second bout of prolonged postoperative ileus.

There were many complicating factors in this case. Pulmonary atelectasis could have impaired her gastrointestinal motility, but the atelectasis resolved well before the gastrointestinal difficulties did. The repeated surgical insults, of course, played a role, but the excessively prolonged postoperative difficulties, the lack of findings at reexploration, and the absence of previous or subsequent gastrointestinal difficulties argue against anatomic factors. Metabolic indexes were carefully monitored while the patient received total parenteral nutrition and were not sufficiently abnormal to account for prolonged ileus and pseudo-obstruction. The use of narcotics for incisional pain ended long before the patient's second operation and was minimal for several days before her final improvement.

We therefore feel that in patients taking verapamil who have unexplained disorders of gastrointestinal motility or apparent bowel obstruction, consideration should be given to the possible contribution of verapamil and an interim trial of its discontinuation. It was only after many days of frustration and puzzlement that this was done in our patient. We report this case to alert more physicians to this possibility so that action may be taken sooner.

Preliminary reports indicate that verapamil inhibits the action of substance P on gastrointestinal motility in dogs[12] and therefore could be useful in the symptomatic treatment of the carcinoid syndrome. Patients with chronic diarrhea due to other causes, such as chronic radiation-induced enteritis, postsurgical short bowel syndromes, or the use of vasoactive peptides, might benefit from involvement in controlled clinical studies of verapamil use.

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Kingella kingae Endocarditis in a Patient With the Acquired Immunodeficiency Syndrome

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Kingella kingae is a rare cause of bacterial endocarditis. Only 24 cases have been reported,[1-3] and 75% of these have been diagnosed in patients with either prosthetic heart valves (33.3%), congenital heart disease (16.7%), or valvular heart disease (25%).[1-3] In four of the reported cases, the patients were immunocompromised. We report the first case of *K kingae* endocarditis in a patient with the acquired immunodeficiency syndrome (AIDS).

Report of a Case

The patient, a 34-year-old woman, was admitted to hospital because of headache, fever, and photophobia. She became ill ten days earlier when painful oral ulcers, attributed to the herpes simplex virus, and cervical adenopathy developed with right ear pain. Two days before admission, the patient had temperatures to 38.9°C (102°F), rigors, myalgias, and a persistent headache accompanied by a stiff neck, photophobia, nausea, vomiting, and vertigo. Immediately preceding admission, a painful lesion developed on the fifth distal phalanx of her left hand, which prompted her to seek medical attention.

For three years, the patient had lymphadenopathy, hairy leukoplakia, chronic diarrhea, weight loss, and recurrent herpes simplex virus ulcers. She was subsequently diagnosed with AIDS based on meeting the criteria for the chronic wasting syndrome in conjunction with a serologic test positive for the antibody to the human immunodeficiency virus. Three months before admission, her T-helper cell count was 188 cells per μl (normal >450). She had no history of endocarditis or rheumatic heart disease, but she had had a diastolic heart murmur since age 19, documented by an echocardiogram three months before admission to be aortic insufficiency. Her medications at the time of admission included trazodone hydrochloride, perphenazine, and flurazepam hydrochloride for the treatment of schizoaffective disorder. The patient had abused cocaine and amphetamines intravenously until 1984 and said she had not used them since. She had a 15-pack-year history of smoking (a pack-year is the number of packs per day times the number of years) and occasionally consumed alcohol.

On physical examination, she appeared ill and displayed mild tardive dyskinesia. Her blood pressure was 96/60 mm of mercury, and the pulse rate was 100 beats per minute. The temperature was 40°C (104°F). The patient had diaphoresis, and her skin was flushed. A 3-cm circumferential, tender, purpuric lesion was present on the distal fifth phalanx of her left hand. There were no skin rashes, splinter hemorrhages, or Janeway lesions. Her fundi were not visualized owing to severe photophobia. Her neck was stiff with decreased flexion. She had white plaques on the edges of her tongue with no evidence of gingivitis. There were two small, nontender anterior cervical nodes. Her point of maximal impulse was diffuse and sustained in the fifth intercostal space 2 cm lateral to the midclavicular line. Two heart murmurs were auscultated: a II/VI systolic ejection murmur at the left sternal border and a II/VI diastolic decrescendo murmur at the left lower sternal border. Other than signs of meningismus as indicated earlier, the results of a neurologic examination were nonfocal.

Laboratory values included a total leukocyte count of 8.3×10^9 per liter with a differential count of 0.87 neutrophils, 0.10 lymphocytes, and 0.03 monocytes. The hemoglobin concentration was 6.89 mmol per liter (11.1 grams per dl) and the platelet count 235×10^9 per liter with normal prothrombin and partial prothrombin times, electrolytes, blood urea nitrogen level, creatinine concentration, and urinalysis results. The chest radiograph was normal. An electrocardiogram showed sinus tachycardia with normal intervals.

A lumbar puncture was done and showed an opening

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CSF = cerebrospinal fluid
HIV = human immunodeficiency virus
IV = intravenous

(Kerlikowske K, Chambers HF: *Kingella kingae* endocarditis in a patient with the acquired immunodeficiency syndrome. West J Med 1989 Nov; 151:558-560)

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pressure of 190 mm of water with clear, colorless cerebrospinal fluid (CSF) containing 0.03×10^9 per liter leukocytes with 0.98 neutrophils, 0.01 lymphocytes, and 0.01 monocytes. The CSF glucose level was 3.4 mmol per liter (62 mg per dl) and protein 0.34 grams per liter. A Gram's stain of the CSF showed no organisms, and the CSF was negative for cryptococcal antigen.

The patient was initially treated with penicillin G, 4 million units in an intravenous (IV) loading dose, then 2 million units every four hours IV; nafcillin sodium, 1.5 grams every four hours IV; and gentamicin sulfate, 1 mg per kg body weight every eight hours IV for presumed aortic valve endocarditis and bacterial meningitis. In 24 hours, four out of four blood cultures were positive for a gram-negative rod. The penicillin therapy was discontinued on the second hospital day, and a regimen of ceftazidime was started. An echocardiogram with Doppler evaluation showed moderate aortic regurgitation without evidence of vegetations on the aortic, mitral, or tricuspid valves. A computed tomographic scan of the patient's head was normal, and the CSF culture was sterile.

The patient was treated days 2 to 4 with a regimen of nafcillin, gentamicin, and ceftazidime and was afebrile after three days of antibiotic therapy. On day 5 of her hospital course the gram-negative rod was identified as *K kingae* based on the original criteria established by Henriksen and Bovre in 1976.[4] This species was sensitive to all antibiotics tested by Kirby Bauer susceptibility including penicillin, ampicillin, and ceftriaxone.

A regimen of ceftriaxone sodium, 2 grams IV a day, was begun on day 5 and discontinued on the 15th day of antibiotic therapy because of a suspected drug rash. Treatment with ampicillin, 2 grams IV every four hours, and gentamicin, 1 mg per kg IV every eight hours, was started on day 15 of therapy and continued for two more weeks. The patient received antibiotic therapy for a total of four weeks. Blood specimens collected on days 2 and 15 of antibiotic therapy and three weeks after completion of treatment cultured sterile.

Discussion

Kingella kingae is an infrequent commensal of the nasopharynx. After examining 437 nasopharyngeal cultures, Henriksen identified five isolates as *K kingae.*[5] Since 1982, the Centers for Disease Control have identified 96 isolates of *K kingae* from 75 known sources in the following distribution: 46% from blood, 28% from bone and joint, 19% from the throat, 1% each from pustule, wound, and urine, and 3% from an unknown source.[6] As noted, most isolates have been from sources that are usually sterile.

Investigators have suggested that the mode of entry of *Kingella* species that leads to infection of sterile body fluids is through disrupted oral mucosa.[7,8] A review of the literature by Wolff and co-workers indicated that 5 of 16 (31%) patients with *K kingae* endocarditis had a history of dental work, gingivitis, or stomatitis preceding the development of endocarditis.[2] Claesson and associates reviewed 33 cases of infections caused by *K kingae,* which included osteomyelitis and diskitis (nine cases), endocarditis (ten cases), septic arthritis (ten cases), occult bacteremia (three cases), and phlegmon (one case). Of these patients, 14 (42%) had a history of recent or current mucosal lesions in the upper respiratory tract. In our review of the literature, 7 of 19 (37%) cases of *K kingae* endocarditis, which includes the patient presented here, had a history of disruption of the mucosal barrier of the mouth.[1,2,8]

Although the ability of *Kingella* species to invade a disrupted mucosal barrier probably contributes to the pathogenesis of *K kingae* bacteremia, preexisting cardiac disease appears to be the primary predisposing factor for the development of endocarditis. Our patient had a history of aortic insufficiency, which is consistent with the observation that 75% of patients with *K kingae* endocarditis have previous valvular damage, prosthetic valves, or congenital heart disease.[1-3]

Wolff and colleagues have also suggested that patients who are immunocompromised may be at an increased risk for *K kingae* endocarditis. They describe four patients who are immunocompromised: two with systemic lupus erythematosus, one with liver cirrhosis, and one taking corticosteroids for the postpericardiotomy syndrome.[2] It is significant that both patients with systemic lupus erythematosus had a history of valvular disease from Libman-Sacks endocarditis before infection with *K kingae.*[9,10] The patient who was taking corticosteroids for the postpericardiotomy syndrome had a mitral prosthesis at the time of infection.[2] The patient with liver cirrhosis had no known history of preexisting valvular or congenital heart disease but did have gingivitis at the time *K kingae* was contracted. Therefore, all four patients had other known predisposing factors, such as disruption of the oral mucosal barrier, previous cardiac valvular damage, and a prosthetic heart valve, that have been associated with *K kingae* endocarditis in addition to the presence of an immunodeficient state.

In the patient presented here, there was a documented immunodeficiency caused by HIV. A reasonable hypothesis is that alterations in the production of mucosal immunoglobulin A or the defects in both cell-mediated and humoral immunity, which have been reported in HIV-seropositive patients and AIDS patients, enhance a susceptibility to bacteremia from *K kingae.*[11] Our patient, however, also had two of the above-described predisposing factors for *K kingae* endocarditis: a history of cardiac valvular damage and oral ulcers. Based on the five reported cases of immunodeficient patients with a history of *K kingae* endocarditis, it is not possible to discern the contribution of an immunodeficient state in predisposing patients to *K kingae* endocarditis.

Arterial embolization is a common feature of *K kingae* endocarditis. In general, about a third of patients with subacute endocarditis will be diagnosed with sequelae resulting from arterial embolization.[12(p1589)] From our literature review, 11 of 22 (50%) patients with *K kingae* endocarditis had evidence of arterial embolization based on the manifestation of a cerebrovascular accident, Osler's node, or a splinter hemorrhage.[1-3,13-15] Wolff and co-workers reported that 6 of 17 (35%) patients with *K kingae* endocarditis had a cerebrovascular accident as a complication of endocarditis.[2] Our patient had an Osler's node.

Kingella kingae endocarditis has been successfully treated with ampicillin, penicillin, and either of these antibiotics plus an aminoglycoside.[1,2] Only one case has been reported in which only a cephalosporin was used for the initial treatment of prosthetic valve *K kingae* endocarditis.[2] The patient was administered cefoperazone sodium, but on day 20 of treatment became febrile, and the drug was changed to penicillin with the successful eradication of *K kingae.* Our

patient was afebrile with a normal leukocyte count after termination of treatment with ceftriaxone on day 15 of therapy. Blood specimens collected before ampicillin and gentamicin therapy was instituted cultured sterile, and the patient had responded clinically. This suggests that ceftriaxone might be useful for treating native valve *K kingae* endocarditis.

In summary, *K kingae* is an occasional inhabitant of the mouth that has a particular propensity to infect previously damaged cardiac valves, prosthetic heart valves, or congenitally damaged hearts. Alterations in the oral mucosal barrier may predispose patients to *K kingae* bacteremia and subsequently endocarditis if preexisting valvular or cardiac damage exists. Because all five patients described as immunodeficient were successfully treated for *K kingae* endocarditis, we would infer that an immunodeficient state may not result in increased mortality and that the 92% cure rate—2 deaths during treatment of endocarditis in 25 reported cases—for *K kingae* endocarditis may be similar for immunocompetent as well as immunodeficient patients.[1,8] Because only five cases of *K kingae* endocarditis in immunocompromised hosts have been reported, however, the definitive contribution of the immunodeficient state to promoting the pathogenesis and pathophysiology of *K kingae* is not known. The use of ampicillin, penicillin, or either antibiotic with an aminoglycoside will cure *K kingae* endocarditis. The number of cases is insufficient to know the actual effectiveness of using third-generation cephalosporins to treat *K kingae* endocarditis.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

The Peer Review Process

To THE EDITOR: The article by Dippe and colleagues in the July issue[1] is misleading about the practice of peer review under the Peer Review Organization (PRO) program and inaccurately characterizes how PROs review for necessity of admission to hospital, with the attendant risk of fostering the belief that PROs are big brothers following a mythical set of ironclad rules. A review of how PROs actually evaluate the necessity of an admission should help to correct any misunderstandings.

First, the article inaccurately describes how criteria are used. Nurse reviewers indeed use the InterQual "Severity of Illness" and "Intensity of Service" criteria but only as screens to identify possibly unnecessary admissions. The authors state, "Admission of a Medicare patient can be denied if the patient does not meet both [of the criteria]." This implies an admission must "meet" criteria to be approved. In fact, quite the opposite is true: an admission must substantially fail all criteria to be considered a possibly unnecessary admission.

When an admission fails all criteria, it is then referred by the nurse to a physician for review. It is key to understand that the physician reviewing the case does not use "criteria" at this point. He or she must use clinical judgment. The physician's task is to answer this question: Was it prudent, necessary, and appropriate to admit the patient at that point in time to the hospital? If the answer is yes, the admission is approved. It is also important to understand that any physician who reviews Medicare cases for a PRO is, by federal mandate, a licensed, actively practicing physician. The PRO program represents true peer review.

There also seems to be misunderstanding about when a denial is final. A single physician does not determine a final denial, as could be inferred from the article. The first physician reviewer's concern leads to a notice of a proposed admission denial, to which both the hospital and the attending physician may respond. If either party responds, a second, independent physician reviewer then reviews the chart, as well as any arguments the attending physician and hospital may make to justify the admission. Only if the second physician reviewer concurs is the denial notice issued. While this is technically called a final denial, the hospital, the attending physician, and in most cases the patient have yet another opportunity (the reconsideration process) to present information that may justify the admission. Thus, three physicians—and in some cases, even more—must independently agree that an admission was unnecessary before there is no further recourse with the PRO.

The peer review process is subjective, and it is unlikely that this will ever cease to be the case. But clinical medicine is also subjective, and it is far from clear that subjectivity is a problem in the peer review program. Indeed, it may well be one of the best features in that it increases discussion and consideration among peers. The peer review process may be imperfect, but I submit that PRO practices in 1989 are substantially more equitable than those described in this study of 1986 cases.

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REFERENCE

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* * *

Drs Dippe and Bell Respond

To THE EDITOR: Before responding to the letter by Dr Mann, a few comments are needed. The tone of Dr Mann's letter suggests that our article was meant to criticize peer review organizations. We believe that PROs in general try to be fair and equitable, that the reviewers hired by the PROs are themselves interested in maintaining high quality of care. In addition, we believe that our own peer review organization, the Health Services Advisory Group, also tries its best to maintain high quality peer review.

Clearly, the Medicare criteria are *not* ironclad rules, and we did not interpret it that way in our study. The criteria are stipulated, however, and are read by the reviewers. How those criteria are applied to each individual case varies with the independent reviewer. It would be foolish to assume that the criteria are interpreted equally by all the reviewers, and it would be equally foolish to assume that the criteria are fixed in stone. We did not state that Medicare admissions would be denied if they did not meet the criteria, rather that nurse reviewers could forward the case to a physician reviewer for a decision if the case did not meet the criteria.

Unfortunately, Dr Mann stated our premise incorrectly as it relates to the final disposition of denial. We clearly state that in 1986 the physician was given the opportunity to explain the reason for the patient admission, and if the explanation was adequate, the admission was approved. Even if the denial took place, it could be overturned successfully. Also, we would have to agree with Dr Mann that the process of review has not only changed but has improved.

Finally, we interpret a sense of hostility—or perhaps frustration—in Dr Mann's letter. We apologize if we have offended anyone involved in the review process; however, we believe the goals set by Dr Mann and ourselves are indeed similar. We want the best possible care given to our elderly, and peer review organizations should try their utmost to ensure high quality care and at the same time reduce unnecessary admissions.

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Are They Really Serious?

To the Editor: About every four months, a professional sports team celebrates the glory of winning a world championship—in their dressing room and on worldwide television. Team members scurry in and out of the picture either "chug-a-lugging" a magnum of champagne or pouring the bubbly liquid over the heads and into the eyes of league officials, teammates, and reporters while millions watch. Within weeks of this event, the team issues a brief announcement that one or more of its star players are being treated for substance abuse. Meanwhile, the commissioner, a team representative, and the team physician declare on national talk shows that they have alcohol abuse under control.

Major league sports have spearheaded extensive anti-substance abuse campaigns, but they at the same time have permitted and tolerated the slobbering of alcoholic beverages while millions of potential alcohol users observe. Both players and management have failed to send a strong message to the public that alcohol need not be a part of winning.

Previously, I cautioned that professional athletes "dipping" snuff tobacco on television would increase sales of the carcinogenic product.[1] Now it is time for the medical community to point out that associating victory with alcohol use may also increase consumption.

If major league sports organizations are really serious about sending a message to curb alcohol and drug abuse, now is the time to denounce and ban the unprofessional drinking and drenching of personnel and reporters on television.

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REFERENCE

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Oral and Intramuscular Ceftriaxone for Meningococcal Infections

To the Editor: We would like to take this opportunity to correct a statement made by Dr Wright in an article on meningococcal infections in the January 1989 issue.[1]

Wright refers to a study by Abramson and Spika,[2] stating that "cultures of the upper respiratory tract in 28.6% of children were positive a week after completing intravenous ceftriaxone therapy for meningococcal disease."

In fact, the patients referred to in this study were treated with intravenous ampicillin and chloramphenicol and/or intravenous penicillin, not ceftriaxone.

Schwartz and colleagues[3] have conducted a study comparing a single dose of ceftriaxone to multiple doses of rifampicin in the eradication of group A *Neisseria meningitidis.* They compared the efficacy of a single intramuscular dose of ceftriaxone to the use of oral rifampicin (four doses in two days) during an outbreak of meningococcal meningitis. Pharyngeal specimens were taken for culture before and one and two weeks after administration. A total of 347 case contacts were enrolled; 179 received ceftriaxone (a single 250-mg intramuscular dose for adults or 125 mg for children), and 168 received rifampicin (600 mg for adults and 10 mg per kg per dose for children twice a day for two days). At one week, the eradication rates for ceftriaxone and rifampicin were 97% and 75%, respectively; at two weeks they were 97% and 81%, respectively. No serious side effects were reported with the use of either agent.

Judson and Ehret report on a study involving 38 patients with gonorrhea who were carrying *N meningitidis* in the posterior pharynx.[4] Patients were randomly assigned to receive (in a 2:1 ratio) either ceftriaxone (a single 125-mg dose) or spectinomycin hydrochloride (2 grams in one intramuscular injection) for the treatment of anogenital gonorrhea or confirmed recent exposure to gonorrhea. All 29 patients treated with ceftriaxone were cured of their meningococcal carriage compared to only one of nine treated with spectinomycin.

We hope these comments clarify the situation.

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Emboli From the Heart

To the Editor: The discussion by Dr Stratton in the August issue on left ventricular thrombi and atrial fibrillation as common causes of emboli from cardiac sources was excellent.[1] Unfortunately, the title was misleading; it should have read "Common Causes of Cardiogenic Emboli (rather than Cardiac Emboli)—Left Ventricular Thrombi and Atrial Fibrillation." Cardiac emboli are emboli lodged in the heart, such as coronary embolism. Cardiogenic emboli are emboli from the heart.

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Treating Otitis Media

To the Editor: I read with interest the article by Dr Borgenicht, "A Matter of Trust," in the August issue.[1] Far too many children who have had suppurative otitis media with effusion have gone on to have active chronic otitis media, meningitis, brain abscess, and death. I most clearly recall a child with otitis media who went on to develop bacterial meningitis and had a stroke. Now, in addition to being paralyzed on one side of his body, he is totally deaf.

While there is some room for variation in style of practice, there is no doubt that antibiotics—traditional, not herbal—and microsurgery have greatly reduced the compli-

cations of suppurative otitis media with effusion. I would have advised the family to start the child immediately on an appropriate antibiotic. I would have made that recommendation quite strongly and had them sign an agreement in the chart if there was any concern that they might not follow my advice. Part of our job as physicians is to sort out for patients fact from fiction. We must advise them if we think they are being inappropriately treated. If this child's course had gone any differently than it did, at least in California, the author would have had a hard time justifying his treatment in front of a review board of his peers or—worse yet—a jury.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Data Analysis for Clinical Medicine: The Quantitative Approach to Patient Care in Gastroenterology

Edited by Thomas C. Chalmers, MD, Distinguished Physician, Boston Veterans Administration Medical Center; Lecturer and Member, Technology Assessment Group, Harvard School of Public Health, Boston; and President and Dean Emeritus, Mt Sinai Medical Center, New York. International University Press, The Old Ribbon Mill/Pitt St, Macclesfield Cheshire SK11 7PT, England, 1988. 214 pages, $49 plus $5 for postage and handling.

This is a book born of the desire to integrate the quantitative sciences of biostatistics and epidemiology with the practice of clinical medicine. To this end, the authors set out to cover the basics in such a way as to be useful both in clinical decision-making and in the performance of clinical research.

The initial chapters serve as introductory forays into complex areas. The introduction to biostatistics touches upon the concepts of sampling, comparison of point estimates, estimation of required sample size, and rudimentary linear regression. The next chapter summarizes measuring disease frequency, measuring association, the concept of confounding factors, and the distinction between observational and experimental study designs. In a short section entitled "Four Simple Questions to Explore the Validity of Nonexperimental Epidemiologic Studies," the authors pose questions applicable to all readers of the medical literature faced with the necessity of evaluating the worth of a published study.

The sections on clinical decision analysis and on clinical trials serve as an excellent introduction to those subjects; the chapter on meta-analysis is one of the strongest in the book, covering the topic in a comprehensive yet practical manner not readily found in other sources. The descriptions of the Mantel-Haentzel-Peto and the Cochran-Dersimonian-Laird methods and the demonstrations of their application are outstanding and particularly relevant as they draw from examples in the gastroenterologic literature. The chapter on searching the medical literature using computers, while a valiant effort at demystification, probably would be best communicated verbally or by actual demonstration to the clinician by a research librarian.

A floppy disk accompanies the text. While perhaps not as easy or self-explanatory as might have been intended by the authors, it does offer a demonstration of the analyses referred to in the book. The user, then, has the option of examining analyses done with the given data sets or of attempting analyses on his or her own data sets. The accompanying chapter in the text, while inspiring in its communication of the simplicity of running computer-guided analyses, might perhaps be slightly intimidating to those not finding the task as easy as promised.

The last section of the book is composed of detailed analyses of five clinical controversies in the field of gastroenterology. Distillation of large amounts of published material on these subjects, as well as the attempt to present the material in such a way as to allow future additions to the data set as further progress is made in these areas, will serve gastroenterologists well.

This text represents a remarkably successful attempt to facilitate for the practicing physician the integration and application of analytic and quantitative skills. By forging a path that will allow clinicians to understand, gain access to, and analyze available information, the authors serve to foster the more widespread application of the tenets of clinical research. In this sense, although targeted toward the practicing gastroenterologist, the book may serve as a model for clinicians in all fields.

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Commentary

Genes and Dreams

JAMES SANTIAGO GRISOLIA, MD, *San Diego*

As I step off the plane in Madrid, a curious feeling of familiarity washes over me. Olive-toned Spanish faces, pungent smells, and the sound of Castilian accents echo and resonate, tugging at the subconscious with the insistent force of childhood memories of summer vacations in the streets and beaches of my grandparents' native Valencia. There is a visceral sense of connectedness, of coming home to this strange land.

Another flight then takes me from Madrid to Valencia, where my father, Santiago Grisolia, a physician researcher in biochemistry, is hosting a workshop in International Cooperation on the Human Genome Project. I promised to attend the meetings, compelled, of course, by a sense of filial duty but also by curiosity. Genome projects are remote from my work as a clinical neurologist, but genetic research appears with increasing frequency in the clinical neurology journals. Besides, the human genome project holds its own special appeal for the nonscientist, perhaps playing on some desire for order and connectedness within ourselves.

This workshop, held October 24 to 26, 1988, in a beach hotel just outside Valencia, was about dreaming the undreamable: complete mapping and sequencing of the entire human genome. During the past decade, interest in tackling this massive project has spawned multiple parallel efforts in many countries. In Valencia, at the bright interface of teeming shore, cerulean sky, and the placid Mediterranean (the great integrator of commerce, culture, and ideas for the ancient world), more than 200 scientists, administrators, and dreamers came together to examine the current state of research. Intense international interest explained the presence of four Nobel Prize winners and the head of the United States National Institutes of Health. There is no single human genome project; no single country has the money or scientific manpower to complete the work by itself. Separate research is funded by the United States Department of Energy, the National Institutes of Health, the National Science Foundation, the Howard Hughes Medical Institute, and by the European Common Market, the United Nations Educational, Scientific, and Cultural Organization (UNESCO), and numerous other government and private centers. One hope in organizing this workshop was that knowledge would be compiled in joint data banks and that needless duplication would be avoided.

Even before Watson and Crick revealed the mystery of the deoxyribonucleic acid (DNA) double helix, the chromosomes were held to contain the Word, the complete book of instructions for life itself: All the important physical determinants of our miraculous selves were thought to reside in a single set of directives, ancient and mysterious as a scroll or tablet in a long-forgotten language.* The double-helix concept struck science like a lightning bolt striking the darkened planet's surface, briefly revealing with daytime clarity the surrounding landscape, illuminated by the stark, alien light of an idea whose fire was its simplicity. Other ideas, including details of gene transcription and regulation, have slowly emerged since then, less incendiary than the double-helix model itself, perhaps more like the brief sputterings of a match lighted in a vast, darkened library. The library of the haploid human genome contains 3 billion pairs of nucleic acid bases. If these base-pairs were letters in a Bantam paperback, the genome would fill 12,000 books of 100 pages each. With all the efforts of molecular genetics, we have so far read and understood less than one tenth of 1% of the ancient library, the equivalent of 12 undemanding Western novels. But rapid advances in automatic sequencing, in computerized data handling and access, and in cell hybridization and cloning techniques now raise the hope that with further advances, the genome can be completely mapped and sequenced over perhaps 10 to 15 years.

Within the scientific community, some say that the genome should not be completely mapped. One reason is that as much as 90% of the chromosomes appear to contain random, useless base-pair sequences, reminding us of Borges's infinite "Library of Babel" where most books had only garbled, meaningless data. Apparently, genetic mechanisms lead to repetitive copies within the same organism of successful gene sequences, and, with generations of recopying, most of these copy sequences acquire random errors and lose meaning, their ancient significance lost as if at the hands of senescent monks, hastily recopying the old library onto fresh parchment with each new generation's birth. As long as one volume or more survive correctly transcribed, random changes in other volumes promote the subtle variations that permit evolution (occasionally one of the mad capuchins accidentally produces a fresh panegyric, suggesting a new theme for the greater glory of the Word). But most of the altered sequences gradually degenerate into what appears to be meaningless chaos—bits of verse, laundry lists, telephone books, soup-can labels from our saurian past. For this

*Among physicians, neurologists are aware that this concept has undergone some relativistic adjustment. Our cells are actually ecosystems, with mitochondria and other organelles the domesticated descendants of invading microorganisms of yore, carrying genetic material of their own. Several neurologic diseases, including Kearns-Sayre syndrome and other mitochondrial myopathies, are inherited through defects in the mitochondrial chromosomes and not through nuclear genetic material.

(Grisolia JS: Genes and dreams. West J Med 1989 Nov; 151:564-566)

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reason, certain authorities argue that sequencing these arid stretches of random DNA would be a waste of time and resources.

But the genome mappers yearn to understand the entire library, not just those sections that appear immediately serviceable. Perhaps important secrets lie hidden in the vast, uncharted stretches of "junk DNA"—hidden genes or unsuspected regulatory mechanisms. Even if the random DNA contains no hidden secrets, understanding the entire genome sequence may reveal how the chromosomes coil and fit together, creating the right geometry for enzymes to dance lightly over the DNA chains, transcribing and repairing the chromosomes' delicate strands at the proper loci.

To physicians, the dream of mapping the genome permits many other dreams to float to consciousness. Complete maps of genetic markers will hasten our understanding of genetic diseases. An abnormal gene identified in, say, Huntington's chorea could be rapidly defined by flanking markers and more quickly sequenced, transcribed, and its daughter protein studied. All diseases with a hereditary component must result in part from abnormal proteins or an abnormal regulation of protein synthesis. Even polygenic diseases with important environmental components such as alcoholism and other psychiatric diseases must depend on abnormal gene products. Understanding these diseases at the basic level may permit specific therapy that would be more effective than symptomatic treatment. Just as polio vaccine replaced the iron lung, perhaps specific therapy will someday mothball our psychiatric wards.

The abnormal gene has already been cloned and the protein synthesized for several single-gene diseases, including Duchenne's and Becker's muscular dystrophy, sickle cell anemia, factor VIII deficiency hemophilia, β thalassemia, chronic granulomatous disease, phenylketonuria, and retinoblastoma. Other single-gene diseases such as cystic fibrosis, Huntington's chorea, and polycystic kidney disease have been localized adjacent to certain markers, although not as well characterized as the diseases above. Work on Alzheimer's disease is yielding interesting insights: This disease, at least in familial forms, is localized to chromosome 21, the same chromosome involved with Down's syndrome, characterized by an Alzheimer's-like late degeneration. Some molecular support exists for a genetic difference between senile and presenile forms.

As our knowledge grows, the demand for genetic screening and counseling will explode. For example, in Huntington's chorea the precise genetic locus is not yet determined. Adjacent markers are known, however, that do not relate to Huntington's disease itself but that do vary in families. By studying the pattern of markers in an affected patient, it is often possible to predict the disease in asymptomatic relatives before any clinical symptoms arise.

The availability of presymptomatic genetic screening for Huntington's chorea and other diseases will require careful counseling before and after results are imparted, much like the counseling physicians are now learning to do for persons undergoing human immunodeficiency virus (HIV) serologic testing. The need for genetic counseling, principally related to birth defects, is already growing and is now met largely by nonphysician geneticists. Clinical geneticists are developing a board examination to document competence in clinical counseling, but eventually primary care physicians will need to assume some counseling duties themselves and to interface with these new nonphysician providers.

In the longer run, additional issues will arise. Will screening for polygenic susceptibility to atherosclerosis be part of the well-child physical examination in the next century? Early diet therapy may become a staple of the school lunch program for selected persons. Will genetic susceptibility to multiple sclerosis permit special antiviral vaccine programs in childhood? Will insurance companies and employers be permitted to discriminate on the basis of genetic information, as they now do for tobacco use, or will such information be closely safeguarded, as are the results of HIV serology testing? Will genetic screening for alcoholism and psychiatric illness permit more enlightened societal attitudes toward these illnesses, or intensify discrimination? As more testing becomes available, physicians will have to advise patients and family and interpret results of testing for teachers, employers, and the court systems.

Among the most exciting therapeutic possibilities to arise from the study of genetics is the concept of gene splicing—using genetic means to insert new genes into an organism's DNA. For example, inserting genes to produce hypoxanthine-guanine phosphoribosyltransferase into cells of newborns suffering from the Lesch-Nyhan syndrome would repair the defect that causes all the manifestations of the disease. Will it be possible to treat inherited or even acquired cancer by inserting fresh genetic directives into the cancer cells, thus bringing unchecked neoplastic growth under control? Certainly, this elegant therapy holds great promise of replacing the controlled barbarism of cancer chemotherapy, but many issues arise regarding the long-term effects of tampering with human DNA, sending through the human gene pool unintended ripples that may bring side effects bobbing to the surface in generations to come. One solution is to prohibit DNA splicing in germ cells. This would confine initial trials to one person's body cells so that any unintended mutations would not pass to future generations.

Politicians, scientists, and laypersons are beginning to grapple with questions about genetics, and physicians must now become aware of these issues as well. Down through time, physicians have been friends, comforters, and explainers to their patients. In this century, biomedical science raced across the fields of ignorance as hungry flames devouring dry chaparral, and the physician's role has grown. Now patients must be protected not only from the ravages of their illness but also from the terrifying aspects of medical technology, whether open-heart surgery, intensive care support, hemodialysis, or other terrible splendors of the biotechnical age. The physician's role as comforter and commonsense interpreter will not change with advances in genetics. At the policy-making level and in the consulting room, physicians will help the human consequences of molecular genetics to evolve, recognizing that the good or evil use of such knowledge rests in humanity's collective hands.

In Valencia, the workshop participants touched on these themes amid a wealth of technical communications regarding the progress and techniques of gene mapping. The human resonance of this work was not lost on my father or the other workshop organizers, who devoted special sessions to ethical, policy, and clinical ramifications. In the final session, the scientists participated in a group discussion and passed by voice vote a number of recommendations regarding progress and the sharing of genetic information. A

most pleasant and courtly man, James Wyngaarden, MD, then head of the National Institutes of Health, collated these recommendations into a document called the Valencia Declaration of the Human Genome.

The Valencia Declaration promotes international cooperation, with the Human Genome Organization (HUGO), designated to coordinate scientific efforts. Information from genome mapping should not be held as trade secrets for economic gain but shared freely among scientists. The declaration encourages continued public debate on the ethical, social, and legal implications of using genetic information, recognizing that answers will evolve in these domains only as fast as new scientific information frames the questions to be asked.

This unique document arose from the awareness and humanity of a unique group of scientists. Acutely aware of the implications of genetic research, both Spanish and international press had laid siege to the entire meeting and eagerly awaited the final policy document as soon as they heard rumor of its gestation. I helped Dr Wyngaarden in a small way to develop the English version of the Declaration, then translated it into Spanish in the pressroom, only to have the document literally snatched from my hands by jostling Spanish reporters for rapid dissemination through electronic synapses of the news media, flashing across continents in the blink of an eye.

Gossamer DNA strands bind us to each other and to our animal past, enmeshing us in our biologic matrix more tightly than chains of iron. The hemoglobin that carries iron-bound breath in our bloodstream has an ancient past, traceable now through subtle changes in the gene sequence from one species to another down evolution's chain to humanity. Hemoglobin's iron core is constant, immutable, but the living link to the primeval past reaches us through the surrounding protein structure, genetically determined. Other genes show similar links to the rest of the biosphere. This enriching connectedness, the surprising discovery of the familiar in unfamiliar surroundings, tugs at the subconscious, providing the most seductive appeal of the human genome project.

The dream of opening the ancient library and unlocking its secrets holds both terror and great promise. In Asimov's "The Nine Billion Names of God," a computer program helps Tibetan monks catalog all the names of God, a task they believe provides the sole rationale for the world's being. The monks' work of centuries is sped to days by computer, and as the final names are printed out, the stars overhead begin winking out.

Like the terrified computer programmers, our species stands at a momentous threshold. Our curious simian nature will propel us through that door. As we contemplate the fragile, gossamer beauty of the ancient library within, our task is to learn without destroying.

Radiologic Case

Superior Mediastinal Mass With Hypertension

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 36-year-old man presented for evaluation of an abnormal chest x-ray film taken as part of a routine physical examination (Figure 1). For the past six months he had had mild dyspnea on exertion and occasional night sweats. He had labile hypertension, first noted ten years previously, but was otherwise in good health.

On physical examination his vital signs were normal and there was no palpable lymphadenopathy. Pulses in all four extremities were similar, as were the blood pressures, which were in the range of 140/90 mm of mercury. Because of the findings on the chest film, further examinations were done.

What is the differential diagnosis?

What examination would you do next?

(SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION)

Figure 1.—A routine chest film shows an abnormal contour of the left superior mediastinum.

(Connolly JP, Maguire FE, Bailey H: Superior mediastinal mass with hypertension. West J Med 1989 Nov; 151:567-568)

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DIAGNOSIS: Pseudocoarctation of the aorta

THE CHEST X-RAY FILM (Figure 1) shows a mass in the left superior mediastinum. The differential diagnosis would include thyroid masses, lymphoma, teratoma, and vascular anomalies, as well as benign or metastatic adenopathy. Computed tomography (CT) or magnetic resonance imaging scans of the chest (or both) are the best modalities for evaluating and differentiating these lesions. If a thyroid mass is suspected, thyroid nuclear medicine scans are also helpful. A CT scan was done (Figure 2), and this showed no evidence of a mediastinal mass. Because of the CT and chest film findings, coarctation and pseudocoarctation of the aorta were considered the most likely possibilities. An arch aortogram (Figure 3) showed the typical findings of pseudocoarctation.

Pseudocoarctation of the aorta is a rare congenital malformation that is characterized by elongation of the aortic arch, which becomes located high in the mediastinum, and associated buckling or kinking of the isthmic portion of the aorta in the region of the ligamentum arteriosum. This is thought to result from less than normal embryonic compression of the third through the seventh dorsal aortic segments. The resulting long arch then twists or kinks at the level of the ductus arteriosum. The crucial characteristic differentiating this condition from true coarctation of the aorta is the lack of a significant pressure gradient across the kink. Rib notching, delayed femoral pulses, decreased lower extremity blood pressures, and prominent collateral vessels are not present in patients with pseudocoarctation because there is no hemodynamic abnormality. The lack of a measured gradient across the lesion at angiography confirms the diagnosis.

Many abnormalities have been reported in association with pseudocoarctation. These include a bicuspid aortic valve, a sinus of Valsalva aneurysm, atrial septal defect, ventricular septal defect, transposition of the great vessels, patent ductus arteriosus, aortic stenosis, hypertension, and Turner's syndrome. These are similar to the abnormalities associated with true coarctation, and this has led to speculation that pseudocoarctation is merely a benign variant of the coarctation spectrum. As in this patient, hypertension has been reported in association with pseudocoarctation, but this is probably due to the expected occurrence of essential hypertension in some patients with the anomaly.

Pseudocoarctation is generally considered to be a benign condition because most patients have no symptoms or signs of hemodynamic compromise. There is some evidence, however, of increased morbidity and mortality, usually related to the associated anomalies described above. Cases of associated saccular and dissecting aortic aneurysms have been reported, and there is one report of radiologic progression and increased mortality in a small group of patients. Therefore, it is probably best to exclude associated lesions in patients discovered to have pseudocoarctation and to observe affected persons who do not require treatment.

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Figure 2.—A computed tomographic scan of the chest shows no evidence of a mass in the superior mediastinum.

Figure 3.—The arch aortogram shows a high aortic arch and "kink" in the proximal descending aorta, typical findings of pseudocoarctation.

Information

Magnetic Resonance Imaging Versus X-Ray Computed Tomography—Which Is the Appropriate First Imaging Examination?

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EXPLOSIVE GROWTH in the use of magnetic resonance imaging (MRI) during the past five years has occurred almost exclusively because of the vastly superior tissue information offered by MRI and because of its wide acceptance by referring physicians.[1] X-ray computed tomographic (CT) scanning is also useful in certain areas of imaging and under certain conditions. The difficulty for physicians often lies in determining which examination is likely to provide the most information for a specific anatomic region or a specific disease category.

Brain and Cranial Imaging

It is now clear that MRI is much more sensitive to small discrepancies in tissue-water content than x-ray CT. Spatial resolution of MRI is at least as good as and in many cases better than x-ray CT. This is particularly the case when imaging areas of the body that have a low inherent patient or physiologic motion. Magnetic resonance imaging is now the most appropriate initial imaging examination for diagnosing neurologic disease in ambulatory and cooperative patients.[2-4] A small proportion of patients having severe claustrophobia, patients with cardiac pacemakers or other nonremovable bioelectronic devices, and patients with known intracranial ferromagnetic aneurysm clips or ferromagnetic particles within the eye are generally unsuitable for MRI. Cranial trauma is often best imaged using x-ray CT because these patients tend to be uncooperative. Acute hemorrhagic lesions are probably diagnosed equally well with either method. Fractures are better visualized with x-ray CT. Tumors, infections, infarctions, and malformations are all visualized with much greater sensitivity using MRI.

The introduction of Food and Drug Administration-approved gadolinium-DTPA (gadopentetate dimeglumine, Magnevist, Berlex Inc) has provided a method of imaging abnormalities of the blood-brain barrier with greater sensitivity than using iodinated contrast with x-ray CT. This means that not only is conventional MRI more sensitive for detecting pathologic disorders than x-ray CT with and without intravenous iodinated contrast, but MRI when used with gadolinium-DTPA becomes still more sensitive and at least as specific for identifying disease processes. In addition, there appears to be no significant morbidity or mortality associated with the use of gadolinium-DTPA in comparison with the known hypersensitivity risk of using iodinated contrast agents with x-ray CT.

Diseases of the Ears, Nose, and Throat

The preferred method for imaging the ears, nose, and throat is more difficult to define because both MRI and CT generally are quite capable, but one method may have slight advantages in certain regions or disorders. Sometimes the characteristics of the two examinations are complementary and each will offer information that is useful for clinical evaluation. For instance, because there is a high degree of inherent physiologic motion in the neck region associated with breathing and swallowing as well as vascular movements, x-ray CT with contrast still tends to be the preferred method for examining the spread of neoplastic disease and identifying lymphadenopathy associated with cancer. Frequently in a cooperative patient, however, MRI can be considerably more beneficial in showing the exact extent of disease and defining infiltrative changes between the muscle planes. In other areas, such as when examining for acoustic neuroma and examining the nasopharynx and paranasal sinus cavities, MRI is notably superior, particularly when used with gadolinium-DTPA. The bony elements of the skull base and the mastoid and petrous portions of the temporal bones, however, are much better visualized with x-ray CT using special bone reconstruction software techniques.

Spine

Considerable experience has now shown that localized high-resolution surface coil MRI of the spine is the preferred method for examining patients for disc disease and degenerative spinal changes with encroachments on the spinal canal or neural foramina. This is particularly true in the thoracic and lumbar spine areas. In the cervical spine it depends somewhat more on technique and equipment because high-resolution views are required to adequately evaluate the cervical neural foramina because of their size and lack of fatty content. The extent of tumors that affect the spine, whether they are osseous, extradural, intradural, or within the spinal cord, is evaluated with much greater precision and facility using MRI. Osteomyelitis and diskitis are readily diagnosed by characteristic signal changes noted with MRI. Their extent and encroachment on the spinal canal structures are easily evaluated. Congenital malformations of the spine including meningomyelocele, tethered cord, and diastematomyelia are all readily evaluated without x-ray exposure. X-ray CT or myelography is only rarely required to further evaluate a questionable finding that may be noted using MRI of the spine. Although MRI as a single examination is more expensive than traditional x-ray CT methods of examining the spine, it is more cost-effective than the typical use of myelography augmented with CT. In children, MRI requires the use of careful sedation techniques or possibly general anesthesia. Few MRI installations are adequately equipped for the use of general anesthesia, but careful sedation techniques can be used at most installations, particularly those that are hospital-based. The successful examination of children using

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x-ray CT or myelographic techniques, unfortunately, also requires sedation or anesthesia. Severe scoliosis can make planar imaging techniques of all types, both CT and MRI, more difficult, although newly developed three-dimensional postprocessing imaging manipulations will probably allow much better evaluation of complex curvature abnormalities.

Musculoskeletal

Magnetic resonance imaging is becoming the imaging method of choice for evaluating the extent of disease for both soft tissue and osseous neoplasms and infections. The replacement of normal bone marrow with infiltrative tumors or infection is more accurately evaluated with MRI. Joints, particularly knee, shoulder, and wrist, are now excellently defined using high-resolution MRI. In particular, normal and diseased menisci and cruciate ligaments of the knee are better and more directly visualized than with any other examination technique except possibly arthroscopy. The lack of invasion of the joint when using MRI is a substantial advantage to many patients. Arthrography is less expensive but also is less accurate and much more uncomfortable.

Pelvis

Because most of the structures within the pelvis are relatively stationary, MRI is an excellent means for evaluating pelvic mass lesions including abnormalities of the bladder, uterus, and rectal area. There has been some difficulty in distinguishing benign from malignant disease within the prostate even when using high-resolution surface coil imaging. Magnetic resonance imaging, however, still appears to be the best method for showing early extracapsular spread of a prostatic malignant tumor as well as being an excellent method of evaluating early pelvic lymphadenopathy.

Abdomen

Imaging of the abdomen using MRI has been difficult because of the considerable motion of the abdominal organs during respiration and by motion artifacts from flowing blood and peristalsis. The liver may be an exception. Special techniques for the liver have shown that MRI can be at least as accurate and may be in some instances more accurate than CT for evaluating the liver for metastatic disease and other neoplasia. The evaluation of renal neoplasms for extension into the renal veins or inferior vena cava is another area wherein MRI may be valuable because of its sensitivity to flowing blood. Currently the best use for MRI of the abdomen appears to be in attempting to answer questions that may occasionally arise during an x-ray CT examination of the region.

Chest

X-ray CT is still the method of choice for examining the lungs and mediastinum for metastatic disease or other soft tissue masses even though MRI can often detect or visualize these lesions. Magnetic resonance imaging is not as sensitive as CT because of chest motion.

Heart

Although cardiac MRI is useful as a research tool, specialized electrocardiographic gated sequences, cineradiographic sequences, and real-time, high-speed echoplanar imaging are rapidly improving. The heart and great vessels can be evaluated with MRI even though this is often not the preferred method for the initial examination. Magnetic resonance imaging of the heart may be helpful for evaluating questions that arise at cineangiocardiography or cardiac ultrasonography. In the future, cardiac MRI may be used for demonstrating flow characteristics across cardiac valves and for evaluating the differential motion of the cardiac musculature, as well as for aiding in the three-dimensional visualization of congenital cardiac defects.

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Lessons From the Practice

Transitions

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Ted had gone.

Crippled and wasted by parkinsonism and heart disease, he died swiftly and painlessly. Joan, his wife of 50 years, sits by the bedside, gently stroking his hair. We feel his presence fill the room.

She turns to me and says, "Say goodbye to Ted, Dr Norcross. Say 'goodbye.' "

I hesitate for a moment, touch his hand, and whisper, "Goodbye, old friend."

Her hand caresses his cheek, but her eyes are clear, her voice steady.

"He had a good life . . . didn't he, Bill?"

Joan is never certain whether to call me Bill or Dr Norcross and so uses both at her whim. She comes from a generation unaccustomed to calling physicians by first names, even physicians 40 years younger than she.

"He had a wonderful life."

It is true.

Ted was a strong and brilliant man: jaunty, ebullient, full of the force of life. Even in old age, withered in his wheelchair, the glint in his eye, the wry smile betrayed a man in whom that last laugh would not fade easily. Ted told me: "For God's sake, shoot me if I get to the point where I'm pissin' on my feet." He chuckled, but I read the reality behind the grin. I told him I didn't own a gun. We laughed. We understood each other. I knew my turn in the wheelchair was coming soon enough.

Ted was a writer, a member of "The Lost Generation" in postwar Paris. He once told me, "You remind me of Hemingway: big, barrel-chested. But you aren't always punching me!" For many years Ted wrote for *The New Yorker* and produced screenplays for television in its early years. It was in Manhattan that he met Joan.

"Do you believe in afterlife, Dr Norcross?" She carefully closes Ted's eyelids.

Once again, I am Dr Norcross. After a decade as their physician, I have become accustomed to this, though I still have no inkling as to why in one moment I am "Dr Norcross" and the next I am "Bill."

"Yes, but not an eternity of sitting on a cloud playing a harp."

Mercifully, she does not ask me to explain.

The brilliant, incongruous sun shines through the window; evening's long fingers begin to reach across the city.

"Why are we here, Dr Norcross?"

Don't do this to me, Joan. Don't make me reach back to my tormented adolescence and search anew for meaning to my existence. I've got a wife and three kids; you know that. I'm a physician. I jog at lunch. I do the best I can.

I breathe deeply.

"I don't know, Joan. What do you think?"

"I think we're here to live our lives to the fullest . . . to take care of one another . . . to love . . . and I think Ted did all those things."

The first tear comes—mine.

We both know that her life is rapidly changing. She seems in perfect health: 76 years old but fit, lean—a former Broadway dancer and Hollywood actress, she can still bend over, legs straight, and place both palms on the floor. But I know she is not long for this world. Not suicide—not for Joan. Still, I see the flame of her existence flickering, dimly, in this darkening room.

I hear the myriad sounds of the ward outside the door, far away, as if from another time. I see Joan, darkly, still holding Ted. She has only him and her memories. Only memories. No children. Few friends. Me.

"You can go now, Bill."

Am I dismissed? I know better. Joan knows, without words, that I want to be here. She wants to be alone with Ted.

I see Joan as a young woman—beautiful, confident. I see her in a movie with Humphrey Bogart. ("*Mister* Bogart was such a gentleman, such a professional," she told me.) She is young, her skin smooth, her mouth smiling. The sun drops behind the coastal fog; Venus sparkles prophetically above the horizon.

"I will call you tomorrow, okay?"

"Okay."

I hold her hand.

The room is black; she wants it that way. The quiet is piercing.

"Goodbye, Joan. Goodbye, Ted."

Instead of going home, I take the elevator to the sun deck on the roof of the hospital. There is no wind, no sound. I am alone. The great canopy of the universe expands before me: the city unfolds to the sea, the sea to the sky, the sky a billowing palette of resplendent stars, motionless to me yet hurtling at unimaginable speeds, incomprehensible distances away. Orion, old friend of my youth, midwinter's comfort—not even you are eternal.

Soon I come to realize what has drawn me here. I have come, privately, to celebrate Ted's life. I find it impossible to grieve his death. He would not want grief from those who cared for him, not after a life of celebration. Ted was one of those rare people who lived before he died.

I feel Ted's spirit returning to the cosmos. I feel a part of it remaining with me.

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Lessons From the Practice

The 'Art' of Medicine

NANCY GRAY STEVENS, MD, MPH, *Seattle*

Dr Jones practiced general medicine until well into her 70s. On retirement, she took up painting as a serious hobby, developing it into a major expressive outlet that persisted even after several strokes, suffered while she was in her 80s, impaired other abilities. Worsening osteoarthritis, residua from the stroke, and incontinence eventually led her and her family to decide that a nursing home was the only workable living arrangement for her.

Dr Jones was medically stable, took few medications, and changed little from month to month, but psychologically she suffered greatly from her loss of freedom and faculties. She was now in her 90s, all of her friends and her generation of family were dead, and she longed to be back in her son's home. As her family physician, I visited her monthly. Each time, she and I talked about her losses, her frustrations, and her limitations. Throughout, painting remained her sole pleasure. The nursing home agreed to allow her to paint. Her room was pleasant and modern, the staff encouraged her painting, and her situation seemed agreeable.

One afternoon her daughter-in-law called me in distress: the nursing home had forbidden Dr Jones to paint in her room. The same afternoon the nursing home called, requesting a mental health referral for her. I decided to visit and assess her mental status myself. As I entered the nursing home that afternoon, I noticed that Dr Jones was the "resident of the month." Her photograph and several of her paintings were displayed prominently in the main hallway. I stopped to talk with the nursing staff. They confirmed that the administrator and nursing supervisor had decided not to let Dr Jones paint in her room. In fact, that was why they requested the mental health referral: Dr Jones was having a hard time adjusting to the decision. The nurse's assessment was that the new wing of the home was the administrator's "baby." She had visited one day and seen a small amount of acrylic paint on a bedspread and on the linoleum floor. The only compromise offered by the nursing home was to allow Dr Jones to paint in the physical therapy room while it was staffed during the afternoon. It was located in the area of the nursing home housing the most severely demented and disabled residents; patients were crying out, and the smell from chronic incontinence was unpleasant. I imagined myself as Dr Jones, facing all the losses in her life, and thought, "I couldn't paint here."

I found my patient despondent. She resisted getting up in the morning; she had no appetite and felt hopeless about the future. She began to weep as we talked about her painting. When I asked about the physical therapy room, she said simply, "Painting requires inspiration."

Leaving the nursing home, I reflected with dismay at how little autonomy Dr Jones had at the end of her life. The institution was her home, and yet she had no power to influence its decisions. My medical training could contribute little to her care. Her family had offered to pay for cleanup, to provide a rug to protect the floor, and to compensate the home for any expenses incurred from Dr Jones's painting, all to no avail. I called the nursing supervisor to discuss the problem and was treated rudely. She felt Dr Jones was being "manipulative" by refusing, after trying it, to paint in the physical therapy room. Finally, I put my thoughts into a letter to the nursing home administrator. After describing my understanding of the situation, I concluded:

> We can't do much medically for Dr Jones; her deficits from her stroke are permanent. Her problems with incontinence and unsteadiness make it unlikely that she will ever leave a long-term care facility. Her future happiness rests with us. The problem, as I see it, is how to give this human being as pleasant an end to her life as we are able without unduly compromising the safety and property of others. Her family seem more than willing to make whatever arrangements are necessary. Surely there is some mutually satisfactory solution to this problem.

I never received a reply to my letter. The next month when I visited, I worried in what state I would find Dr Jones. To my delight I found her happily settled into a private room, the walls bedecked with her paintings. She told me proudly that her paintings now decorate one of the home's common rooms. On a rug in the middle of her room was an easel holding her current work-in-progress, a bright impressionistic landscape with splashes of colorful flowers.

At the age of 95 Dr Jones suffered another stroke and died. Remembering her now, I am struck by how easily this otherwise exemplary nursing home forgot how life seems to a patient, by how little freedom disabled residents have within their existing abilities, and by how quickly the staff requested a mental health referral to help this patient adjust to change rather than questioning the change itself. I wonder if we, as physicians, don't have a special responsibility to protect the potential of institutionalized patients to function at the most autonomous and free level of which they are capable. I feel certain that in the five years I was Dr Jones's physician, helping restore her freedom to paint was the biggest contribution I made to her health and quality of life.

(Stevens NG: The 'art' of medicine. West J Med 1989 Nov; 151:572)

From the Research Section, Department of Family Medicine, University of Washington School of Medicine, Seattle.

Reprint requests to Nancy Gray Stevens, MD, MPH, Assistant Professor, Department of Family Medicine, University of Washington School of Medicine, Seattle, WA 98195.

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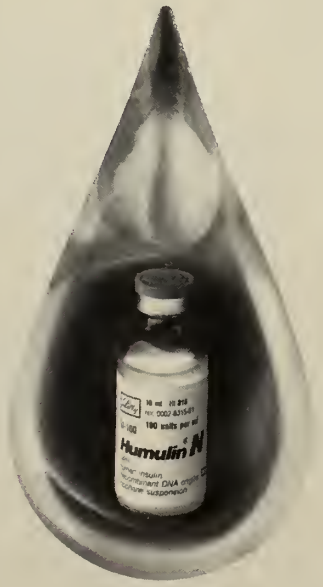

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CONTINUING MEDICAL EDUCATION

(Continued from Page 513)

April 14—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sun. 8 hrs. $175. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

November 1989-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 1989-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 38 hrs. $1125. Contact: UCSD.

October 27-28—**Artificial Knee Conference.** UCI at Center for Health Education, Long Beach. Sat-Sun. 11 hrs. Contact: UCI.

November 13-15—**21st Annual Surgical Congress.** Orange County Surgical Society at Le Meridien Hotel, Newport Beach. Mon-Wed. 16 hrs. Contact: OCSS, PO Box 1297, Orange 92666. (714) 978-3983.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. Contact: UCD.

January 22-26—**13th Annual Assembly in Surgery.** UCSD at Catamaran Resort Hotel. Mon-Fri. Contact: UCSD.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

OF INTEREST TO ALL PHYSICIANS

October 19-21—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 19-21—**Occupational Low Back Pain Conference.** UCI at Queen Mary Hotel, Long Beach. Thurs-Sat. Contact: UCI.

October 21—**9th Annual Norman Sharrer Symposium: Common Difficult Treatment Syndromes.** Kaweah Delta District Hospital at Holiday Inn, Visalia. Sat. 6 hrs. $25. Contact: Kaweah Hospital, 400 W Mineral King Ave, Visalia 93291. (209) 625-7308.

October 28—**Current Concepts in Medicine 1989.** Los Angeles County Medical Association and Antelope Valley Medical Center at Desert Inn Hotel, Lancaster. Sat. 7 hrs. $60. Contact: Sue Crimin, (805) 949-5942.

October 30-November 3—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 31-November 3—**Therapeutic Hotline.** Stanford University Medical Center at Molokai, Hawaii. Tues-Fri. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

November 2-4—**The Challenge of Diabetes.** Annenberg Center for Health Sciences at Eisenhower at Rancho Mirage. Thurs-Sat. 15 hrs. Contact: Registration Secretary, (800) 321-3690.

November 3—**Alzheimers Update.** UCD at Sacramento. Fri. Contact: UCD.

November 6-9—**Primary Care Update: 74th Scientific Assembly.** Interstate Postgraduate Medical Association at Town & Country Hotel, San Diego. Mon-Thurs. 24 hrs. $200. Contact: IPMA, PO Box 5474, Madison, WI 53705. (608) 257-1401.

November 9-11—**Addiction Medicine: State of the Art.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at San Diego. Thurs-Sat. Contact: California Society, 3803 Broadway, Oakland 94611. (415) 428-9091.

November 30-December 2—**California Trauma Conference.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

November 30-December 3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Las Vegas Hilton. Thurs-Sat. 18 hrs. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 2—**7th Annual Reider Laser Center International Pulmonary Symposium on Brachytherapy and Argon and ND: YAG Lasers With ND: YAG Laser Workshop.** UCI at Center for Health Education, Long Beach. Contact: UCI.

December 2—**Lasers in Clinical Medicine: Update 1990 . . . A Parade of Clinical Specialties.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Fri-Mon. 6 hrs. $135. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

December 6—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda at Los Angeles. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC Sepulveda 91343. (818) 891-2473.

December 9-10—**Travel Medicine '89.** American Society of Tropical Medicine and Hygiene at Honolulu, Hawaii. Sat-Sun. 12 hrs. $250. Contact: Linda Limauro, 20 York St, New Haven, CT 06504. (203) 785-2476.

December 11-12—**Clinical Care of the AIDS Patient.** UCSF at Hyatt Regency Embarcadero, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 16-20—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 40 hrs. $295. Contact: UCLA.

January 20—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $110. Contact: Kim I. Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

January 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Kona Surf Resort, Kona, Hawaii. 1 week. 21 hrs. $395. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

January 26-28—**Practical Aspects of Pain Management.** Hawaii Medical Association at Sheraton Kauai Hotel, Poipu, Kauai, Hawaii. Fri-Sun. 16 hrs. $275. Contact: John Dillon, MD, PO Box 457, Kalaheo, Hawaii 96741. (808) 742-6750.

January 26-28—**Pass or Fail? Examining Medical Education and Current Reforms.** Stanford University at Fairchild Auditorium. Fri-Sun. 15 hrs. $15. Contact: Doug Woelkers, (415) 725-2243.

January 27-28—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Holiday Inn Union Square, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

February 1-3—**13th Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Mon-Fri. Contact: UCSD.

February 4-9—**CME Ski Meeting.** Nevada Academy of Family Physicians at Caesars Tahoe Stateline, Lake Tahoe, Nevada. Sun-Fri. 34 hrs. $395. Contact: Dotie Batchelor, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 7-9—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 21 hrs. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 9-10—**Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

(Continued on Page 578)

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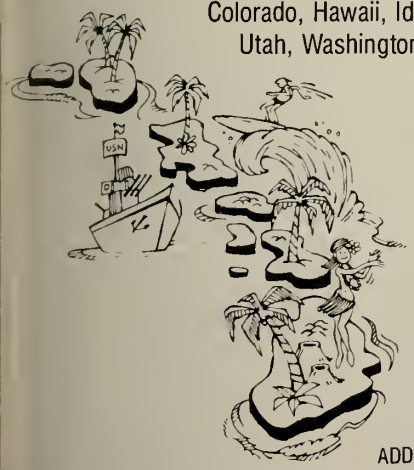

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CONTINUING MEDICAL EDUCATION

(Continued from Page 574)

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 22 hrs. $350. Contact: UCSD.

February 22-24—**The Practicing Physician's Approach to Difficult Headache Patient.** Scripps Clinic and Research Foundation at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

March 2—**16th Annual Diabetes Symposium.** UCD at Hilton Inn, Sacramento. Fri. Contact: UCD.

March 9-10—**Diabetes Update.** UCSF at Stanford Court Hotel, San Francisco. Fri-Sat. 10 hrs. $225. Contact: UCSF.

March 12-15—**Critical Care Medicine: 28th Annual Symposium.** USC at Las Vegas Hilton, Nevada. Mon-Thurs. 27 hrs. $585. Contact: USC.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

March 31-April 7—**Primary Care Medicine.** UCSF at Maui, Hawaii. One week. $475. Contact: UCSF.

IDAHO

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** University of Washington at Sun Valley. Fri-Sun. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 441-9762.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 18—**Affective Disorders.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

December 1-2—**Trauma Update '89.** Clarion Four Seasons, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

December 7-9—**American College of Physicians, New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

January 20—**Neuropsychiatry.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

February 23-25—**18th Annual New Mexico Thoracic Society Lung Disease Conference.** Santa Fe. Contact: Billie Dytzel, American Lung Association of New Mexico, 216 Truman, NE, Albuquerque 87118. (505) 265-0732.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Contact: Psychiatric Medical Assn, (505) 841-3511.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 578)

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 15—**Infectious Diseases.** Seattle. Wed. Contact: NW Hospital, (206) 368-1623.

November 16-17—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 580)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 579)

November 17—**ENT/Ophthalmology.** Tacoma. Fri. Contact: PCMS, (206) 627-7317.

November 17—**23rd Annual Cancer Conference. Innovative Management of Cancer Patients.** Seattle. Fri. Contact: VMMC.

November 29-December 1—**Update on Surgery.** Seattle. Wed-Fri. Contact: U/W.

December 2—**AIDS Issues.** Seattle. Sat. Contact: Evergreen Hospital, (206) 823-7599.

December 6-10—**5th Annual Infectious Disease Conference.** Seattle. Wed-Sun. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 7-8—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

December 8—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 8-10—**Contemporary Practices of Orthopaedic Transplants.** Sun Valley. Fri-Sun. Contact: U/W.

December 9—**Medicine for Attorneys.** Seattle. Sat. Contact: U/W.

December 9-10—**The Anesthesiologists' Environment.** Seattle. Sat-Sun. Contact: WSSA, (206) 441-6020.

January 4-5—**Pediatric Pain.** TBA. Thurs-Fri. Contact: U/W.

January 18—**Law & Medicine Symposium.** Tacoma. Thurs. Contact: PCMS, (206) 627-7137.

January 24-26—**Modern Molecular Biology for Physicians.** Seattle. Wed-Fri. Contact: U/W.

February 1-3—**Medical and Surgical Management of Heart Disease.** Seattle. Thurs-Sat. Contact: U/W.

February 2—**Peripheral Vascular Disease, 1990.** Seattle. Fri. Contact: VMMC.

February 8-9—**Cancer Review 1990.** Tacoma. Thurs-Fri. Contact: PCMS, (206) 627-7137.

February 8-10—**Ophthalmology: Annual President's Meeting.** Seattle. Thurs-Sat. Contact: (206) 441-9762.

February 9-10—**Cardiology Conference.** Seattle. Fri-Sat. Contact: VMMC.

February 28—**AIDS Update.** Tacoma. Wed. Contact: PCMS, (206) 627-7137.

March 3—**AIDS Issues '90.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

March 8-9—**Tacoma Academy of Internal Medicine Annual Review.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

March 9—**Risk and Insurance Management for Physicians in Practice.** Seattle. Fri. Contact: VMMC.

March 15-16—**Primary Care Orthopaedics.** Seattle. Thurs-Fri. Contact: U/W.

March 21-23—**Recent Advances in Cancer Detection.** Seattle. Wed-Fri. Contact: U/W.

March 26-April 6—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Sun. Contact: U/W.

March 29-31—**Trauma and the Elderly.** Seattle. Thurs-Sat. Contact: U/W.

April 6—**A Day of Infectious Disease.** Seattle. Fri. Contact: VMMC.

April 13-14—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: (206) 627-7137.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

WYOMING

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001. 1 (800) 342-7526. ◆

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

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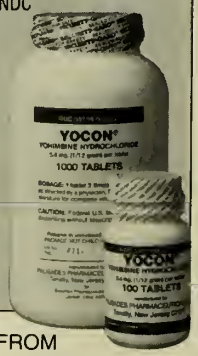
How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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BC/BE INTERNIST being sought to establish practice in resort community of Ruidoso, New Mexico. Beautiful mountain setting with easy access to all forms of recreation. Financial assistance may be available for the right individual. For more details, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy three physician Family Practice group (including OB) seeks replacement for partner departing fall 1989. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

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ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

GENERAL SURGEON. Established young, mellow but compulsive General Surgeon in southern California seeks an associate so he can spend more time with his young children. If interested send CV and personal description to Number 159, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

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BC/BE INTERNIST being recruited for the community of Artesia, New Mexico. Solo practice with cross-coverage available from local Internist. Community-based financial assistance may be available for the right individual. Family oriented community with year round recreation; excellent weather. Fully equipped 38-bed hospital. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

(Continued on Page 582)

(Continued from Page 581)

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of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

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BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

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UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is in the second phase of an ambitious development plan and is searching for physicians residency trained in Emergency Medicine. The Health Sciences campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level I trauma center, has paramedic base station training responsibilities, and has a helicopter service. Emergency Physicians supervise medical students, interns, and residents in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

MD TO ASSIST in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

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(Continued on Page 584)

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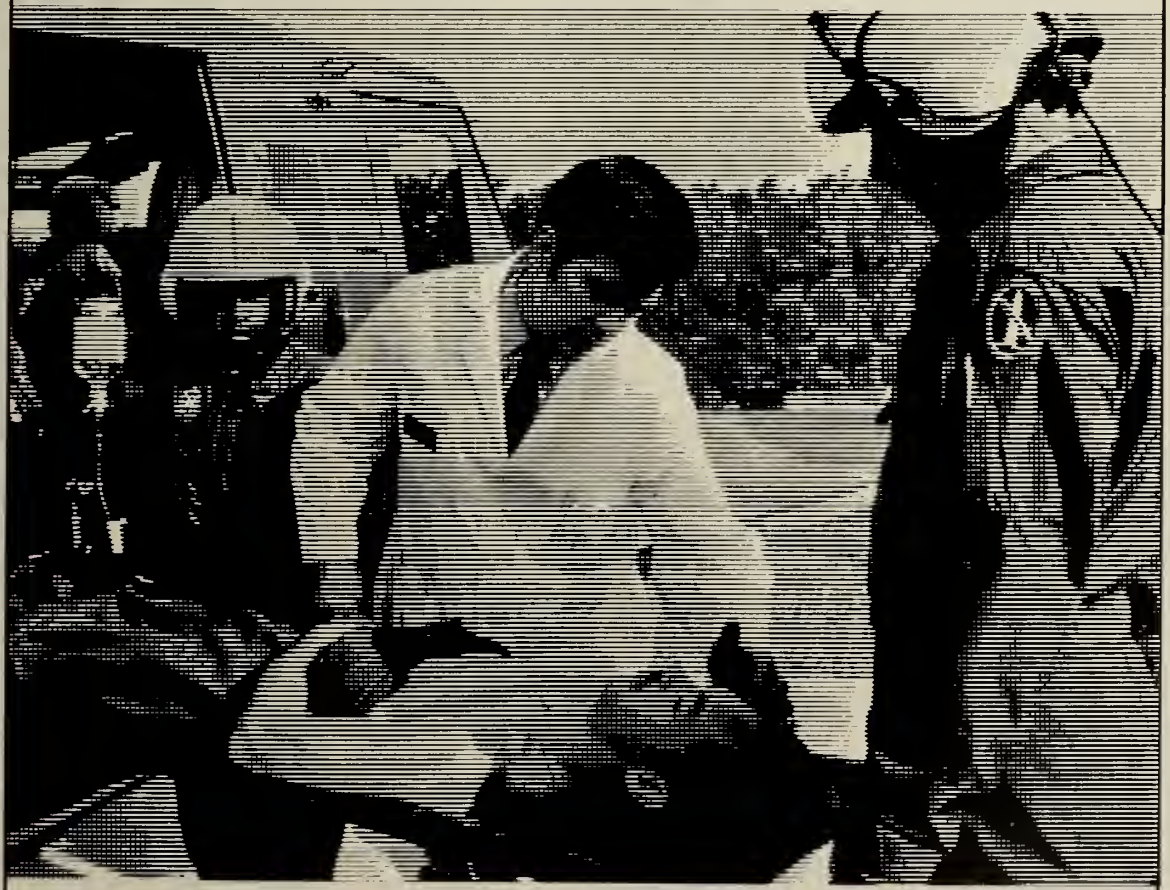

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(Continued from Page 582)

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Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

SAN DIEGO. Well established, multispecialty group composed of Family Physicians, General Internists, OB/GYNs, Pediatricians, General Surgeons, ENT, and Ophthalmologist is expanding. Those interested in joining a vital private practice group, with emphasis in primary care and seeing fee-for-service and managed care patients, are welcome to send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92018; (619) 295-0599.

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- Utilization Review expertise
- Strong interpersonal skills

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Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
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Huntington Beach, CA 92647

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SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

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SAN FRANCISCO. Outstanding opportunity for BC/BE Internist or Family Practitioner at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

COLORADO, WASHINGTON, NORTHERN CALIFORNIA. Exceptional practice opportunities now available in Family Practice, Pediatrics, Internal Medicine, Psychiatry, and OB. Send CV to D. A. Franklin, MD, and Associates, 4894 Sterling Dr, Boulder, CO 80301.

(Continued on Page 585)

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PHYSICIANS WANTED

POSITIONS AVAILABLE
For BC/BE physicians in California and nationwide in the following specialties: ENT, Family, Internal, Neurology, Neurosurgery, OB/GYN, Ophthalmology, Orthopedics, Pediatrics, Urgent Care. Excellent salary/benefits. Private practices also for sale in northern California. Send CV or call **BRADSHAW ASSOCIATES, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762.**

CALIFORNIA. BC/BE OTOLARYNGOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

FAMILY PRACTITIONER, BC/BE for community health center. Excellent opportunity in the culturally rich Four-Corners area of northwest New Mexico. Near 110-bed hospital, four physicians with mid-levels in integrated system of health and human services. Outstanding benefit package. Recreational paradise in community of 30,000. Contact Sheila Brenner, Farmington Community Health Center, PO Box 3239, Farmington, NM 87499; (505) 327-4796.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

GENERAL SURGEON BC/BE sought to join busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC SURGEON BC/BE sought to join two physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ONCOLOGIST NEEDED for multispecialty group practice in Seattle; affiliated with University of Washington. Full-time clinical with potential for research. Diverse patient population includes managed care, fee-for-service, retired and active duty military. Attractive salary plus incentive and excellent benefit package. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

(Continued on Page 586)

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

MARTINEZ

Emergency Physicians — Join friendly, relaxed and highly professional colleagues at our 204-bed hospital in the heart of the San Francisco Bay Area. We are seeking experienced physicians, BE/BC preferred. Locum Tenens and part-time work available Summer/Fall, 1989 & Winter/Spring, 1990. Recent adjustments provide excellent hourly rate plus paid malpractice. Career positions also available, providing salary and excellent benefits package. Send CV to: Ted Bayer, M.D., Chief, or Andrea Wagner, M.D., Asst. Chief, Department of Emergency Services, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1000, ext. 3316 or (415) 372-1124.

Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

FAIRFIELD

Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including scheduled time off, malpractice insurance, medical, dental and life insurance, and a substantial retirement program. Our physicians are free to concentrate on providing quality health care, without the burdens of managing a practice.

To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 585)

PHYSICIANS WANTED

PHYSICIANS/ SURGEONS

Practice opportunities available now in these and other medical/surgical specialties:

FAMILY PRACTITIONER

Live and work in rural areas of Kansas or North Dakota. Generous compensation packages.

ANESTHESIOLOGIST

Clinical/academic position with prestigious Children's Hospital in Southern U.S. for BC Pediatric Anesthesiologist.

GENERAL SURGEON

Women's health center at Central California hospital seeks BC general surgeon. Must support concept of women treating women.

For immediate consideration for these and other opportunities, call collect or send current CV:

HURD/CAMPBELL

Department TWJM
100 East Wardlow Road, Suite 100
Long Beach, California 90807
Telephone (213) 595-1101

SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570** *or send CV to* **Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

PEDIATRICIAN BC/BE sought to join four physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OBSTETRICIAN/GYNECOLOGIST BC/BE sought to join three physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a community health clinic setting near Fresno, California. We offer a contract arrangement with competitive salaries and benefits, malpractice paid. We are affiliated with the UC San Francisco teaching program. Central California has Yosemite National Park, excellent family recreation, low housing costs, with both urban and rural life-styles. Contact Dr Donn Cobb, Health Officer, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

PHYSICIANS WANTED

EMERGENCY MEDICINE OPPORTUNITIES

OREGON • NEVADA • WASHINGTON

Emergency department opportunities, including directorship, are available with Spectrum Emergency Care at the following client hospitals:

Astoria, Oregon:	Located on the Oregon coast. Moderate volume ED. Annual reimbursement $80,000 +.
Tillamook, Oregon:	Located on the Oregon coast. Moderate volume ED. Annual reimbursement $69,000 +.
Fallon, Nevada:	One hour from Reno. Low volume ED. Annual reimbursement $73,000 +.
Boulder City, Nevada:	Half hour from Las Vegas. Low volume ED. Annual reimbursement $69,000 +.
Elko, Nevada:	Located in central Nevada. Moderate volume ED. Annual reimbursement exceeds $80,000.
Yakima, Washington:	Director and staff positions at Osteopathic hospital. Low volume ED/urgent care setting. Annual reimbursement $69,000 +.

As an independent contract physician with Spectrum, you are offered:

- High-limit occurrence malpractice insurance
- Allowance for CME, professional dues, licensure fees, and relocation expenses
- Directors offered annual administrative stipend and health benefits

Call 1-800-288-8044 for details.

ARA services

SPECTRUM EMERGENCY CARE, Inc.

John Brown
1155 Kelly Johnson Blvd., Suite 305 Colorado Springs, CO 80920

CALIFORNIA MULTISPECIALTY. Cardiologist, Anesthesiologist, Infectious Disease Specialist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Pathologist, General/Thoracic Surgeon. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center, 17821 S. Pioneer Blvd, Artesia, CA 90701.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

BC/BE NEUROLOGIST to join progressive San Francisco bay area HMO. Busy clinical practice in desirable Marin County. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Dept of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

ENDOCRINOLOGIST NEEDED to join a busy solo Endocrinologist in a growing southern California city. Established referral base, 300-bed acute care hospital. Competitive salary leading to partnership. Reply with CV to Number 169, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MARICOPA COMMUNITY MEDICINE ASSOCIATES of Phoenix, Arizona, is staffing 60 plus physicians, physician assistants, and nurse practitioners for Maricopa County's ambulatory care clinics at various locations in the Phoenix metropolitan area. General Practice, Family Practice, and Internal Medicine specialist openings. Maricopa Medical Center, Dept of Community Medicine, 4th Floor, 2601 E. Roosevelt, Phoenix, AZ 85008; (602) 267-5288.

SAN JUAN ISLANDS, WASHINGTON. Established, well-equipped 8,500 square foot community-owned clinic with complete emergency facilities seeks two BC/BE ACLS certified Family Physicians. Immediate employment, competitive salaries and benefits. Adjacent 85-bed nursing home. Superb scenic and recreational area. Send résumé to Leonard Eliel, MD, Box 370, Friday Harbor, WA 98250. An EO Employer.

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Internal Medicine, OB/GYN, Occupational Medicine, Orthopedics, General Surgery (breast disease focus), Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

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PHYSICIANS WANTED

NORTHERN CALIFORNIA. Rapidly expanding HMO in the San Francisco bay area is currently seeking three highly motivated BE/BC Family Practice/Emergency Room Physicians for the Urgent Care Center in a career and/or temporary position. Our 228-bed community hospital offers excellent specialty support, flexible hours, and competitive salaries. Career physicians are offered many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV or contact Edward Cheng, MD, Dept of Urgent Care, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119-1197; (408) 972-6110. EOE.

INTERNIST BC/BE needed to join busy pulmonary subspecialty practice in rapidly expanding area near Seattle, Washington. Affiliated with 200 plus-bed and expanding hospital. Other subspecialty welcome, but not necessary. Excellent salary with incentive, benefits, office space, and practice support. Send CV and references to Business Manager, Eastside Pulmonary Associates, 1603-116th Ave NE, Ste #112, Bellevue, WA 98004.

TUCSON, ARIZONA. BC/BE, residency trained Family Physician sought to join busy solo Family Physician in private practice. Attractive start-up package available. Send CV to Herb Jalowsky, MD, 1701 W. St Mary's Rd, Tucson, AZ 85745; (602) 622-1414.

PHOENIX, ARIZONA. Maricopa County, Department of Corrections is seeking Internists, General and Family Practitioners, and Certified Physician Assistants. Prefer experience in adult ambulatory care. Five weeks paid vacation, ten holidays, one week CME. Excellent hours—minimal on call. Paid malpractice. Paid health insurance. Facilities include both infirmary and family practice clinic settings providing a good working atmosphere. Send CV to Maricopa Medical Center, Dept of Community Medicine, 2601 E. Roosevelt, Phoenix, AZ 85008; (602) 267-5288.

CARDIOLOGY. Cardiologist BC/BE to join two other Cardiologists in eight physician multispecialty clinic in Seattle. Extensive invasive/noninvasive opportunities. Send CV to PO Box 364, Seahurst, WA 98062.

CALIFORNIA
FAMILY PRACTICE

Established medical group seeks a BC/BE eligible Family Practice physician to join them in private practice.

Physician would assist in providing full spectrum of Family Practice care, including obstetrics. Competitive salary and benefit program, as well as an opportunity for a partnership in the practice. Send your CV to the attention of:

Cindy Holston,
1237 Rose Avenue,
Selma, CA, 93662
or phone **209/896-6370**

We are located in Central California, where housing costs are reasonable and recreational activities are numerous.

PHYSICIANS WANTED

WASHINGTON STATE
ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY	HEMATOLOGY/ONCOLOGY
CARDIOLOGY	OB/GYN
DERMATOLOGY	RHEUMATOLOGY
INTERNAL MEDICINE	GENERAL SURGERY

FAMILY PRACTICE—permanent, part-time, locum tenens

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

UNIVERSITY PHYSICIANS. Student Health Service, University of Wyoming, Laramie, is seeking physicians for full-time employment. Applicants must have a Medical Doctor's degree plus be BC/BE by either AAFP or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the state of Wyoming. Prefer candidate to have at least four years of primary care experience. Physicians to join two full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. Closing date: October 25, 1989, or until positions are filled. Send inquiries and/or CV to Albert H. Roth, MD, Acting Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, Wyoming 82071. EOE/AA.

ENDOCRINOLOGIST. Outstanding opportunity for a BC/BE Endocrinologist to join busy hospital-based group in Berkeley. Send CV to Randall Ammon, MD, Endocrinology Dept, 3001 Colby St, Berkeley, CA 94705.

ACADEMIC INTERNIST—Los Angeles area—general or subspecialty. Primarily inpatient teaching—Family Practice residents. Full-time. Director, Northridge Hospital Family Practice Residency, 18406 Roscoe Blvd, Northridge, CA 91325.

SANTA BARBARA COUNTY FAMILY PRACTICE

California BC/BE Family Practice Physicians sought by Santa Barbara County Health Department for ambulatory practice in Santa Barbara County. Progressive, up to date, and well supported clinical system. Highly qualified physicians will have two to four years experience in county and/or community based outpatient clinics. Fluency in Spanish is highly desirable. Competitive salary DOE. For more information please send current CV to **Elliot Schulman, MD, Santa Barbara County Health Care Services, 300 N. San Antonio Rd, Santa Barbara, CA 93110; (805) 681-5460.** AA/EOE.

FAMILY PRACTICE. The Kaiser Permanente Medical Group's northern California facility in Napa is seeking a BC/BE Family Practitioner to fulfill general clinic and hospital duties. Members of our large, multispecialty group earn highly competitive compensation and outstanding benefits including malpractice insurance, medical, dental, and group life insurance, vacation, educational leave, an excellent retirement program, and special arrangements for physicians transferring from established practice. For more information, please send CV to B. Parmeter, MD, The Permanente Medical Group, 3284 Jefferson St, Napa, CA 94558. EOE.

NORTHERN CALIFORNIA—San Francisco bay area. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large prepaid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299, or call (415) 742-2516. EOE.

SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY. Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Vallejo, CA 94589; (707) 648-6200. EOE.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

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PHYSICIANS WANTED

FAMILY PRACTICE

CALIFORNIA

Family Practice physicians needed in a progressive community health center located in Central California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacation and time-off policy. Moving and temporary housing allowance to be negotiated. Affiliated with University of California, San Francisco residency program. Position is 60% clinical, 40% teaching. Central California has excellent family recreation, low housing costs, with both urban and rural lifestyles. Send your CV to:

Dr. Donn Cobb, Health Officer
Fresno County Department of Health
P.O. Box 11867
Fresno, CA 93775
209/445-3202

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and is applying to have an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a paramedic base station and training center and, in addition, has an active helicopter service and regional poison center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr. 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after December 31, 1989. The University of California is an Affirmative Action/Equal Opportunity Employer.

INTERNIST BC/BE. Progressive San Francisco bay area HMO has a full-time Internal Medicine position and a part-time Urgent Care position available. Busy clinical practice with facilities in San Rafael and Petaluma. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Dept of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

PHYSICIANS WANTED

NORTH CENTRAL IDAHO

17 physician multispecialty group recruiting BC/BE partners.

- 2nd Dermatologist
- 2nd Gastroenterologist
- 3rd General Internist
- 6th Pediatrician

Progressive medical community. Outstanding recreational area. Excellent life-style.

Send CV to:

Bob Baker, Administrator
Valley Medical Center and Children's Clinic
2318 Vineyard Ave
Lewiston, ID 83501
(208) 746-1383

CARDIOLOGIST—NONINVASIVE/INVASIVE to join four member busy cardiology practice in small town, one hour from Los Angeles. Full range of noninvasive cardiology and active Catheter lab. Position available immediately through July 1990. Send CV to Number 175, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ONCOLOGY/HEMATOLOGY. Excellent opportunity for Hematologist/Oncologist to join busy Hematology/Oncology practice in central California. Work as little or as much as you want. Excellent salary and opportunity for partnership. Reply to Number 174, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PULMONOLOGIST BC/BE (INTERNAL MEDICINE) with skills in bronchoscopy and management of critically ill patients sought to join busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CENTRAL CALIFORNIA (FAMILY PRACTICE). We have an opening for a Family Practice Physician. Clinic is a 17,000 square foot primary care facility located near Bakersfield offering medical, dental, lab, x-ray, and pharmacy services. Excellent salary and benefit package. Call George Johnston, (805) 845-3731, for details or write PO Box 457, Lamont, CA 93241.

WANTED: CLINICIAN/TEACHER to join 14 General Internists at Santa Clara Valley Medical Center and Clinics, a public hospital affiliated with Stanford University. Applicants should be BE (BC if eligible more than two years), love clinical medicine and patient care, enjoy housestaff and medical students, and have excellent sense of humor to deal with usual politics of university-affiliated public hospital/clinic work. Send inquiries, CV to Kent Imai, MD, Chief, Primary Care Division, Dept of Medicine, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128.

PSYCHIATRIST, Northern Arizona University. Progressive, accredited student health center is seeking a Psychiatrist to initiate mental health program. Northern Arizona University is situated in beautiful, mountainous Flagstaff, Arizona, a summer/winter recreation area with skiing, hiking, camping, fishing, and boating. Medical facilities for 14,000 students are located in the modern, spacious health center. This academic staff position is 10 months per year. Please address inquiries to Leonard A. Wright, MD, Director, PO Box 6033, Flagstaff, AZ 86011. NAU is an AA/EOE. Women and minority applicants are encouraged to apply.

PHYSICIANS WANTED

NEUROLOGIST

BC/BE, full- or part-time, for expanding San Francisco bay area private practice with emphasis on clinical Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
240 Polk St
Box 337
San Francisco, CA 94109

RADIOLOGIST. Immediate opening for BC General and Diagnostic Radiologist at military hospital near Seattle. Washington license not required. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (213) 521-6630.

ACADEMIC INTERNIST wanted to teach house staff on clinic and inpatient services at LDS Hospital as a member of its Division of General Internal Medicine. ABIM certification and qualifications for University of Utah faculty appointment required. Must have skills and strong interest in teaching, patient care, and research. Start July 1990. Send CV and three letters of recommendation to Corwin Q. Edwards, MD, Clinic Director, LDS Hospital, 8th Ave and Eighth St, Salt Lake City, UT 84143. An Equal Opportunity Employer M/F/H/V. A Facility of Intermountain Health Care, Inc.

DIAGNOSTIC RADIOLOGIST to join five member group covering two small hospitals in northern California. Call (916) 877-8092.

PSYCHIATRIST. Innovative team working with older adults. Med evaluations, consultations. Some supervision. $78K to $104K plus benefits for full-time. Part-time also available. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

PEDIATRICIANS. At FHP, the nation's largest physician-managed HMO, quality care begins with caring, competent physicians. As a staff physician, you can practice medicine at our Albuquerque medical centers and enjoy competitive salaries with generous benefits. We are currently seeking BC/BE Pediatricians who are quality-minded. Opportunities also are available in Arizona, California, Guam, and Utah. Contact Professional Staffing Dept, 4300 San Mateo NE, Albuquerque, NM 87110; (505) 881-7900 or (800) 444-4347. Equal Opportunity Employer.

ALBUQUERQUE, NEW MEXICO. Physician needed immediately for full-time position in busy Occupational Medicine clinic. Duties include treatment of injured workers, supervision of nurse practitioners, assessment of occupational hazards, etc. BC/BE in Emergency Medicine, Family Practice, Internal Medicine, Occupational Medicine, or Preventive Medicine. Competitive salary and benefits. Send CV to Barry M. Diskant, MD, Albuquerque Industrial Medicine Specialists, PC, 717 Encino Pl, NE, #25, Albuquerque, NM 87102; (505) 842-5151.

BC/BE ORTHOPEDIC SURGEON for beautiful New Mexico mountain community. Camping, fishing, snow skiing, windsurfing, trail-riding, and golf. Low cost of living and high quality of life. Dedicated and compatible hospital staff at progressive JCAH hospital. For further information call Dr Janice Dorn collect, (602) 224-9277, or send inquiry and CV to Janice Dorn, MD, PhD, 4227 N. 32nd St, Ste 108, Phoenix, AZ 85018.

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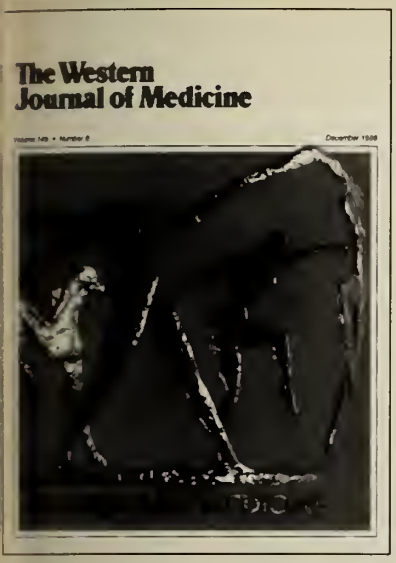
SPECIAL ISSUES



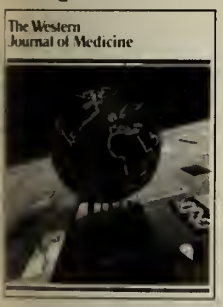
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

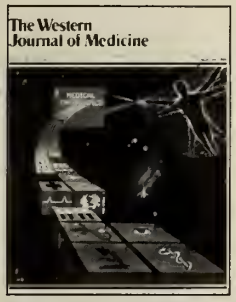
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics

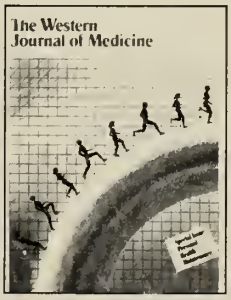


Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine

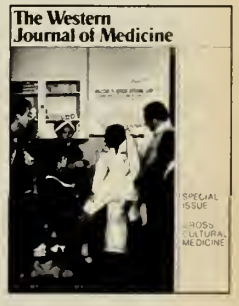
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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(Continued from Page 588)

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INTERNAL MEDICINE OR FAMILY PRACTICE. Solo Internist retiring, office adjacent to one of two hospitals in mid-Puget Sound, city of 65,000 in Washington. Rapidly expanding area. Free parking, equipment, records, and experienced personnel available. (206) 252-1088.

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Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1990, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: November 10-12, 1989, Westin Hotel, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1990, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1990, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1990, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

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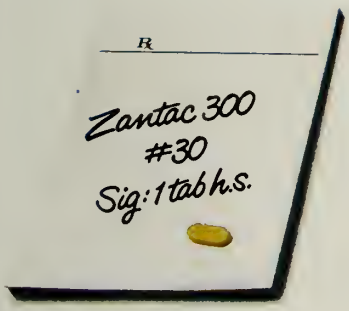

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2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Zantac® 300

ranitidine HCl/Glaxo 300 mg (base)

Glaxo ROCHE

See adjacent page for Brief Summary of Product Information

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In ACE inhibitors

24-hour power* in blood pressure control

Now available on Medi-Cal

Drug Type Codes: 3128-A (5 mg) 3128-B (10 mg) 3128-C (20 mg) 3128-D (40 mg)

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ZESTRIL®!

LISINOPRIL-STUART

*The antihypertensive effect may diminish at the end of the dosing interval.

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INDICATIONS AND USAGE. ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **DRUG INTERACTIONS. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL. **Agents Increasing Serum Potassium:** ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Lithium:** Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. **Human Experience:** There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use the ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality. When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward

support of blood pressure and renal perfusion with the administration of fluids and pressores as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity. Another ACE inhibitor, enalapril, has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n = 2003†) Incidence (discontinuation)	ZESTRIL/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia. (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response.

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Precautions: General. Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Tenex could not be established, should a rash occur, Tenex should be discontinued and the patient monitored appropriately.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n = 279)	Clonidine (n = 278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
N	580	580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

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*The American Academy of Dermatology, the American Academy of Family Physicians, the American College of General Practitioners in Osteopathic Medicine and Surgery, the American Osteopathic Association, and the American Social Health Association.

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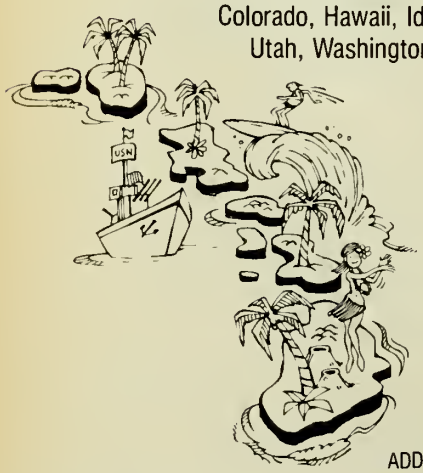

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Women and Medicine

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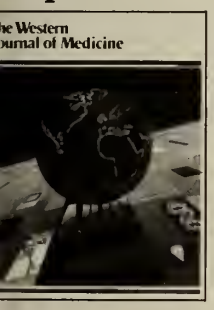
Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

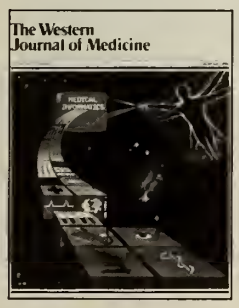
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

AIDS—A Global Perspective



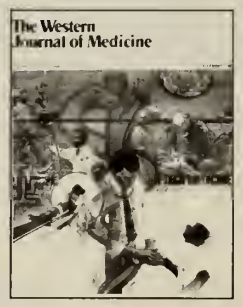
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



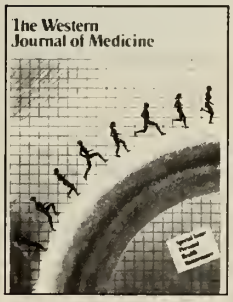
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



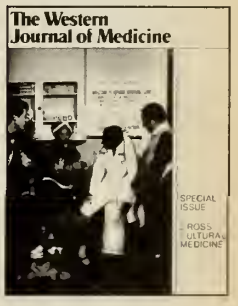
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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Dr Fox is in private practice in Coeur d'Alene and is the Special Editor for Idaho.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

December 15-17—**18th Annual Seminar—Genitourinary Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

January 20—**Current Medical and Surgical Approaches to Urolithiasis.** Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

February 11-16—**International Congress III: Lasers, Stents, and Interventions in Vascular Disease.** Arizona Heart Institute, Scottsdale. Sun-Fri. Contact: Erika Scott, (602) 266-2200.

February 16-17—**Geriatrics in a Changing Society: Enhancing Function—2nd Annual Regional, Multidisciplinary Conference.** Samaritan Institute of Gerontology, Phoenix. Fri-Sat. Contact: Jean Kiernat, (602) 239-5884.

February 23-24—**Mayo Clinic Update on Plastic and Reconstructive Surgery.** Marriott's Mountain Shadows Resort, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

February 23-25—**Anesthesia for the 1990s.** Arizona Society of Anesthesiologists, Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 24—**Diabetes 1990: A Practical Approach to Management IV.** Good Samaritan Regional Medical Center, Phoenix Children's Hospital, and American Diabetes Association at Wyndham Paradise Valley Resort. Sat. Contact: Teri Quesnell, (602) 239-5994.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital. Tues-Fri. Contact: Susan Fraley, (602) 239-5783.

March 1-3—**Rheumatology for the 90s: A Look Into the Future.** Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: CME, Arizona Health Sciences Center, (602) 626-7832.

March 1-4—**A Continuance of Excellence.** Arizona Academy of Family Physicians, The Registry Resort, Scottsdale. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

March 3-7—**Fourth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute of St Joseph's Hospital and Medical Center at Marriott's Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

March 8-10—**Recent Advances in Neurology and Neurosurgery—17th Annual Symposium.** Barrow Neurological Institute at Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, (602) 285-3178.

March 23-24—**Ophthalmic Reviews.** Mayo Clinic-Scottsdale at Scottsdale Sheraton Resort. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

March 27-30—**15th Annual Primary Care Update.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: Lynne Mascarella, (602) 626-7832.

March 29-30—**Clinical Reviews.** Mayo Clinic-Scottsdale at The Registry Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 31—**Nutrition Update for Primary Care Providers.** Arizona Health Sciences Center, Tucson. Sat. Contact: Lynne Mascarella, (602) 626-7832.

June 22-24—**Thirteenth Annual Pediatrics in the Red Rocks.** American Academy of Pediatrics—Arizona Chapter at Los Abrigados, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 11-14—**Anesthesia Update 1990.** UCSD at Hotel Del Coronado, Coronado. Thurs-Sun. 21 hours. Contact: UCSD.

January 14-19—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai, Hawaii. Sun-Fri. 21 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 26-28—**28th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $250. Contact: Katherine Barky, MD, Pediatric Anesthesiology Conference, Children's Hospital, PO Box 54700, Los Angeles 90054.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Sat. Contact: Murray G. Atnikov, MD, PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 5-8—**18th Obstetric Anesthesia Conference.** Ohio State University Hospitals Department of Anesthesiology at Westin, Maui, Hawaii. Mon-Thurs. Contact: Arlene Rogers, 410 West 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 9-13—**64th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Fri-Tues. Contact: IARS, 3645 Warrensville Center Rd, Cleveland, OH 44122-5280. (216) 295-1124.

March 24-25—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott Hotel. Sat-Sun. 9 hrs. $125. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

May 17-20—**California Society of Anesthesiologists 1990 Annual Meeting.** California Society of Anesthesiologists at San Francisco Marriott. Thurs-Sun. 18 hrs. $175. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

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A graduate of the University of Oklahoma, Jeffrey Davis, M.D., joined FHP in 1982 after completing his Family Practice residency at St. Mary-Corwin Hospital in Pueblo, Colorado, and 5 years of private practice in Oklahoma. A member of the American Board of Family Practice, he is now Chief of Staff of FHP Hospital in Fountain Valley, California.

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CARDIOLOGY

January 10-12—**Cardiovascular Disease in the Elderly.** UCI at Fess Parker's Red Lion Resort, Santa Barbara. Wed-Fri. Contact: UCI.

January 19-20—**Coronary Heart Disease Update.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. Contact: Deborah Wilderson, MER, (800) 421-3756.

January 25-27—**Cardiology '90.** Scripps Memorial Hospital at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $325. Contact: Nancy Donegan, 7777 Alvarado Rd, Ste 110, La Mesa 92041. (619) 462-6800.

February 21—**30th Annual Cardiovascular Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. 6 hrs. Contact: Linda Morgado, (916) 891-7300, ext 7375.

February 23-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marquis Hotel, Palm Springs. Fri-Sun. Contact: Deborah Wilderson, MER, (800) 421-3756.

March 30-31—**Cardiology for the Clinician.** UCI at Long Beach. Fri-Sat. Contact: UCI.

DERMATOLOGY

January 18-20—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande at Torrey Pines, La Jolla. Thurs-Sat. $400. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 19-21—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess. Fri-Sun. 20 hrs. Contact: UCSD.

February 21-25—**Problems of the Aging Skin.** Stanford University at Las Vegas, Nevada. Wed-Sun. Contact: Paul Jacobs, Professor of Dermatology, Room R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

January 15-19—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. Contact: UCSD.

January 17-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Maui, Hawaii. Wed-Sun. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 17-20—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Las Vegas, Nevada. Sat-Tues. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

February 18-21—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal Series 3.** Emergency Medical Abstracts at Los Angeles. Sun-Wed. 20 hrs. Contact: Bob Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

March 4-9—**11th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences Inc, PO Box 52 B, Newport Beach 92662. (714) 650-4156.

March 19-23—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott Hotel. Mon-Fri. 32 hrs. Contact: UCSD.

March 21-23—**Advances in Emergency Medicine 1990.** UCSF at Mark Hopkins Hotel, San Francisco. Wed-Fri. 22 hrs. $425. Contact: UCSF.

April 7-14—**Cardiopulmonary Emergencies.** American Postgraduate Institute of Postgraduate Education and Scripps Memorial Hospital Encinitas at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. One week. Contact: Edith S. Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

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April 19-22—**9th Annual Emergency Medicine and Acute Care: A Critical Appraisal, Series 3.** Emergency Medical Abstracts at San Francisco. Thurs-Sun. 20 hrs. Contact: Robert Cowsill, 6917 Royer Ave, West Hills 91307. (818) 884-8844.

May 7-11—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

January 18-21—**Advances in Gastroenterology.** UCSD at Hotel Del Coronado, San Diego. Thurs-Sun. 23 hrs. $425. Contact: UCSD.

January 19-20—**The Medical Dysphagia Team: From Intensive Care to Rehabilitation.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 25-27—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 2-3—**7th Annual Reider Laser-Urology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 3-4—**Searching for New Horizons in Non-Invasive Technology: The Next Decade.** UCSF at Union Square Holiday Inn, San Francisco. Sat-Sun. $200. Contact: UCSF.

February 9-10—**2nd Annual Bristol Myers Symposium on Neurosciences.** UCSD at Price Center, La Jolla. Fri-Sat. 12 hrs. $50. Contact: UCSD.

February 14-16—**23rd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15 hrs. Contact: UCSF.

February 17-21—**Approaches to the Skull Base.** House Ear Institute at Marina Beach Hotel, Marina del Rey, Los Angeles. Sat-Wed. Contact: Antonio De La Cruz, MD, HEI, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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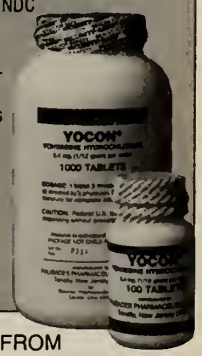

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Non-members, please look for the complete schedule of events and a registration form in our 12-page insert appearing in the December 1 issue of *Annals of Internal Medicine.* Non-members can also call 1-800-523-1546 (extension 2429). In Pennsylvania, call 215-351-2429.

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CONTINUING MEDICAL EDUCATION

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February 18-25—**Emergencies in Internal Medicine.** UCD at Lake Tahoe, Incline Village, Nevada. One week. 23 hrs. $410. Contact: UCD.

February 19-21—**Clinical Hematology and Oncology: 1990.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 26-March 2—**Topics in Internal Medicine.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Mon-Fri. 37 hrs. $475. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 28-March 2—**10th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF Radiation Oncology Course, c/o Crest International, 940 Emmett Ave, Ste 14, Belmont 94002. (415) 595-2704.

March 5-6—**Advanced TMJ Arthroscopy: Rationale, Treatment, and Management.** UCSD. Mon-Tues. Contact: UCSD.

March 7-8—**Advances in Endocrinology and Metabolism.** UCSF at Fairmont Hotel, San Francisco. Wed-Thurs. 14 hrs. $275. Contact: UCSF.

April 18-20—**Advances in Infectious Diseases.** UCSD at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $380. Contact: UCSF.

May 26—**Fine Needle Aspiration Tutorials.** UCSF. Sat. 7 hrs. Contact: UCSF.

OB/GYN

January 28-February 2—**OB/GYN Update: 1990.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 24 hrs. $395. Contact: UCD.

February 2-3—**7th Annual Reider Laser-Gynecology.** UCI at Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

February 15-18—**45th Annual Obstetrical and Gynecological Assembly of Southern California.** Ob-Gyn Assembly of California at Beverly Hilton, Beverly Hills. Thurs-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 21-23—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Marriott Hotel, Newport Beach. Wed-Fri. Contact: UCI.

March 22-24—**Geriatric Gynecology With Special Emphasis on Urinary Incontinence.** UCI at Palm Springs. Thurs-Sat. Contact: UCI.

April 18-20—**Prenatal Genetics Diagnosis and Fetal Therapy.** UCI at Red Lion Hotel, Costa Mesa. Wed-Fri. Contact: UCI.

May 31-June 2—**Advanced Fetal Heart Rate Monitoring.** UCI at Monterey Plaza Hotel. Thurs-Sat. Contact: UCI.

OPHTHALMOLOGY

December 14-15—**Update: Pediatric Ophthalmology.** UCSF at Hyatt Regency, San Francisco. Thurs-Fri. Contact: UCSF.

January 28-February 1—**Squaw Valley Vitreo-Retinal Symposium.** UCD at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Barbara Arnold, MD, 7275 E Southgate Dr, Sacramento 95823. (916) 393-1000.

February 23-25—**American Academy of Ophthalmology Regional Update Course.** American Academy of Ophthalmology at Los Angeles. Fri-Sun. Contact: Gary Holland, MD, 655 Beach St, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

PEDIATRICS

January 12-13—**North American Society for Pediatric and Adolescent Gynecology** at Red Lion Hotel, Costa Mesa. Fri-Sat. Contact: UCI.

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The Western Journal of Medicine

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January 17-20—**Health Science Response to Child Maltreatment 1990.** Children's Hospital and Health Center at U.S. Grant Hotel, San Diego. Wed-Sat. Contact: Children's Hospital and Health Center, (619) 576-4072.

February 2-4—**Current Concepts in Pediatric Medicine 1990.** Children's Hospital at Hyatt Islandia, San Diego. Fri-Sun. Contact: Children's Hospital and Health Center, Medical Education Dept, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 16-18—**Pediatrics in Progress.** American Academy of Pediatrics at Hyatt Regency Embarcadero, San Francisco. Fri-Sun. 16 hrs. $220. Contact: AAP, CME Registration, PO Box 927, Elk Grove Village, IL 60009-0927. (800) 433-9016.

April 6-7—**Annual Ambulatory Pediatrics.** UCD at Hilton Inn, Sacramento. Fri-Sat. Contact: UCD.

April 19-20—**9th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

PSYCHIATRY

December 1989-May 1990—**Mental Research Institute Training Workshops at Mental Research Institute.** Contact: MRI, 555 Middlefield Rd, Palo Alto 94301. (415) 321-3055.

January 21-26—**16th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 25 hrs. $395. Contact: UCD.

February 2-4—**Cognitive Therapy Conference.** University of Pennsylvania Cognitive Therapy and Research Department at Newporter Resort, Newport Beach. Fri-Sun. 16 hrs. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 9-11—**West Coast Psychiatry Board Review.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. 16 hrs. $450. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

February 24-25—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 12 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

April 28-29—**The Cutting Edge 1990—The Heart of the Matter: Helping Improve Relationships.** UCSD at La Jolla Marriott Hotel. Fri-Sat. 13 hrs. $300. Contact: Cass Jones, 7916 Convoy Court, San Diego 92111. (619) 565-9921.

RADIOLOGY

January 26-28—**42nd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 60009-1215. (213) 827-9078.

January 30-February 3—**16th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 1-4—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 16 hrs. $375. Contact: UCSD.

March 2-4—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-7—**Neuroradiology Update.** UCSD at Hotel del Coronado, San Diego. Mon-Wed. 18 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-9—**Combined Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Tues-Fri. 23 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 6-9—**MRI for the Technologist: Symposium and Workshops.** UCSD at Hotel del Cornado, San Diego. Tues-Fri. 21 hrs. $275. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**OB/GYN and Abdominal Sonography: Update 1989.** UCSF at Hyatt Regency, San Francisco. Fri-Sun. 15 hrs. $350. Contact: UCSF.

(Continued on Page 620)

Most patients need only one.

K-DUR™ 20 | Microburst Release System™
(potassium chloride) 20 mEq Sustained Release Tablets

A daily prophylactic dose in a single tablet.

Please see next page for brief summary of prescribing information.

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World leader in drug delivery systems.

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K-DUR™ | Microburst Release System™
(potassium chloride) Sustained Release Tablets

INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE).** There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS);** other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 619)

March 19-23—**33rd Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 32 hrs. $515. Contact: UCSF.

March 26-30—**Diagnostic Imaging: 1990.** UCSF at Kauai, Hawaii. Mon-Fri. 23 hrs. $515. Contact: UCSF.

April 14—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sun. 8 hrs. $175. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 15-20—**10th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Introduction to Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 22-25—**CT and MRI in Body Imaging: A Comprehensive Course.** Tues-Fri. 15 hrs. $515. Contact: UCSF.

SURGERY

December 1989-December 1990—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

December 1989-June 1990—**Microsurgery Training Courses.** UCSD at Grossmont Hospital, La Mesa. 40 hrs. $1125. Contact: UCSD.

January 13-14—**Automated Percutaneous Discectomy Workshop.** UCSF. Sat-Sun. 12 hrs. $800. Contact: UCSF.

January 19-20—**What's New in General Surgery: 12th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. 14 hrs. $210. Contact: UCD.

January 22-26—**13th Annual Assembly in Surgery.** UCSD at Catamaran Resort Hotel. Mon-Fri. Contact: UCSD.

February 23—**Symposium on Retina and Vitreous Surgery.** White Memorial Medical Center New Otani Hotel and Garden, Los Angeles. Fri. 5 hrs. Contact: Farrah Arya, White Memorial Medical Center, 414 N Boyle Ave, Los Angeles 90033. (213) 269-0607.

March 15-18—**10th Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sun. 17 hrs. $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

March 15-18—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County and USC Medical Center at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 7-8—**Automated Percutaneous Discectomy Workshop.** UCSF. Sat-Sun. 12 hrs. $800. Contact: UCSF.

May 16-20—**12th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

OF INTEREST TO ALL PHYSICIANS

December 24-30—**Advances in Medicine '89.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sun-Sat. 16 hrs. $425. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 16-20—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 40 hrs. $295. Contact: UCLA.

January 20—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $110. Contact: Kim I. Leadon, 747 52nd St, Oakland 94609. (415) 428-3021.

January 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Kona Surf Resort, Kona, Hawaii. 1 week. 21 hrs. $395. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 21-25—**Family Practice: Caring and Curing.** Kauai Foundation for Continuing Education and Hawaii Medical Association at Poipu Beach, Kauai. Sun-Thurs. 28 hrs. $450. Contact: David J. Elpern, MD, 3420-B Kuhio Hwy, Lihue, HI 96766. (808) 245-1173.

(Continued on Page 621)

CONTINUING MEDICAL EDUCATION

(Continued from Page 620)

January 26-28—**Practical Aspects of Pain Management.** Hawaii Medical Association at Sheraton Kauai Hotel, Poipu, Kauai, Hawaii. Fri-Sun. 16 hrs. $275. Contact: John Dillon, MD, PO Box 457, Kalaheo, Hawaii 96741. (808) 742-6750.

January 26-28—**Pass or Fail? Examining Medical Education and Current Reforms.** Stanford University at Fairchild Auditorium. Fri-Sun. 15 hrs. $15. Contact: Doug Woelkers, (415) 725-2243.

January 27-28—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Holiday Inn Union Square, San Francisco. Sat-Sun. 10 hrs. $205. Contact: UCSF.

February 1-3—**13th Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Mon-Fri. 21 hrs. Contact: UCSD.

February 4-9—**CME Ski Meeting.** Nevada Academy of Family Physicians at Caesars Tahoe Stateline, Lake Tahoe, Nevada. Sun-Fri. 34 hrs. $395. Contact: Dotie Batchelor, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 5-9—**Occupational and Environmental Medicine III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 5-16—**Occupational and Environmental Medicine I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

February 7-9—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 21 hrs. Contact: Bonny A. Mower, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 9-10—**Infectious Disease.** UCD at Hilton Inn, Sacramento. Fri-Sat. 11 hrs. $165. Contact: UCD.

February 12-17—**UCI Family Practice Refresher Course.** UCI at Newport Sheraton Hotel, Newport Beach. Mon-Sat. Contact: UCI.

February 19-21—**10th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Sciences and Betty Ford Center. Mon-Wed. Contact: Annenberg Center for Health Sciences at Eisenhower, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Princess. Mon-Fri. 20 hrs. $350. Contact: UCSD.

February 22-24—**The Practicing Physician's Approach to Difficult Headache Patient.** Scripps Clinic and Research Foundation at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 24-25—**Advances in the Diagnosis and Treatment of Common Medical Problems.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Sat-Sun. 12 hrs. $150. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

March 2—**16th Annual Diabetes Symposium.** UCD at Hilton Inn, Sacramento. Fri. Contact: UCD.

March 9-10—**Diabetes Update.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 10 hrs. $225. Contact: UCSF.

March 12-15—**Critical Care Medicine: 28th Annual Symposium.** USC at Las Vegas Hilton, Nevada. Mon-Thurs. 27 hrs. $585. Contact: USC.

March 13-18—**Wilderness Medicine: '90.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Tues-Sun. 22 hrs. $395. Contact: Eugene Allred, PO Box 321, Yreka 96097. (916) 842-4667.

March 19-22—**The Best Approach 1990: Effective, Efficient Strategies in Orthopaedics/Sports Medicine, Cardiology, Gynecology, and Infectious Disease.** Group Health Cooperative of Puget Sound at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Thurs. 20 hrs. $325. Contact: GHCPS, CX-5, 201 16th Ave East, Seattle, WA 98112. (206) 326-6262.

(Continued on Page 622)

RISK MANAGEMENT PROGRAMS

Preventing Malpractice in Emergency Medicine: Case Studies

Sheraton at Fisherman's Wharf San Francisco, California
February 2-3, 1990

Co-sponsored by the California Chapter of ACEP

Bad Outcomes May Occur, Malpractice Need Not.

This 2 day course for physicians and risk managers in Emergency Medicine uses actual closed malpractice cases and relevant scientific literature to illustrate the most important and common pitfalls in the practice of Emergency Medicine. Critical components of the history, physical and data collection that are pivotal in assuring a well supported evaluation, assessment and treatment will be identified.

Also included:

- Medical-Legal issues in Emergency Department Activities
- Developing effective Quality Assurance Programs
- Issues in Medical Record Documentation
- Preparing for Deposition and Trial

This course has applied for 12 hours of ACEP Category I credit. Special hotel rates are available for course participants.

For course information and registration, contact:
Risk Management Programs
120 Montgomery Street, Suite 1000, San Francisco, CA 94104 (415) 433-RISK

Upcoming Presentations:

June 11-14, 1990	*Lake Tahoe, CA*
August 28-31, 1990	*Honolulu, Hawaii*
November 14-16, 1990	*Los Angeles, CA*

CONTINUING MEDICAL EDUCATION

(Continued from Page 621)

March 31-April 7—**Primary Care Medicine.** UCSF at Maui, Hawaii. One week. 20 hrs. $475. Contact: UCSF.

April 27—**Alzheimer's Update.** UCD at Beverly Garland Hotel, Sacramento. Fri. Contact: UCD.

IDAHO

July 26-28—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sun. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 8-12—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

January 15-19—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

January 18-19—**Ocular Trauma.** Holiday Inn Pyramid Journal Center, Albuquerque. Thurs-Fri. Contact: Mary R. Boning, Office of Medical Education and Research at Presbyterian Hospital, (505) 841-1225.

January 20—**Neuropsychiatry.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Sat. Contact: Psychiatric Medical Assn, (505) 841-3511.

January 22-26—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 5-9—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 12-16—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

February 23-25—**18th Annual New Mexico Thoracic Society Lung Disease Conference.** Santa Fe. Fri-Sun. Contact: Billie Dytzel, American Lung Association of New Mexico, 216 Truman, NE, Albuquerque 87118. (505) 265-0732.

February 26-March 3—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Sat. Contact: American Educational Institute, (800) 354-3507.

February 28-March 3—**New Mexico Metabolism Symposium.** Taos. Wed-Sat. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 5-9—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 12-16—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 14-18—**Sports Medicine for the Primary Care Physician.** Durango, Colorado. Wed-Sun. Contact: Kathy Sickes, Lovelace Medical Foundation, 2441 Ridgecrest Dr, SE, Albuquerque 87108. (505) 262-7749.

March 17—**Illness Behavior.** Psychiatric Medical Association of New Mexico at University of New Mexico, Department of Nursing and Pharmacy, Albuquerque. Fri. Contact: Psychiatric Medical Assn, (505) 841-3511.

March 19-23—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 26-30—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

March 30-31—**Can OB/GYN Survive Liability?** Albuquerque Convention Center. Fri-Sat. Contact: Mary R. Boning, Office of Medical Education and Research, Presbyterian Hospital, (505) 841-1225.

April 2-6—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

April 9-13—**Medical Malpractice/Risk Management and AIDS Update.** Kanadahar Condominiums, Taos. Mon-Fri. Contact: American Educational Institute, (800) 354-3507.

May 4-5—**103rd Annual Meeting of the New Mexico Medical Society.** Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson, NE, Albuquerque 87109. (505) 828-0237.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 3-6—**Hip and Knee Bioskills Workshop: The Arthritic Hip and Knee** (Sponsor: UUMC). Snowbird. Contact: (801) 581-8664.

January 7-13—**Arthroscopic Surgery 1990** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-7602.

January 13-20—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). Sat-Sat. Prospector Square, Park City. Contact: (801) 581-8664.

January 24-28—**The Immunocompromised Surgical Patient: Mechanisms and Therapy in Burns and Trauma** (Sponsor: UUMC). Wed-Sun. Snowbird. Contact: (801) 581-8664.

(Continued on Page 624)

IS YOUR SPECIALTY WORTH AN EXTRA $8,000 A YEAR?

If you are a resident in anesthesiology, orthopedic surgery, or general surgery—which includes neurosurgery, colon/rectal, cardiac/thoracic, pediatric, peripheral/vascular or plastic surgery—you could be eligible for an $8,000 annual stipend in the Army Reserve's New Specialized Training Assistance Program.

Your skills in one of these specialties are worth a lot to us, so we are offering you the opportunity to use them in a variety of challenging settings, from major medical centers to field hospitals. In addition to your salary as an Army Reserve Officer, you will also receive a monthly stipend.

We realize that a resident's schedule is hectic, so we will be flexible about the hours you serve. You could serve as little as two weeks a year now, with a small obligation later on.

If you would like more information about this stipend program, or about other medical opportunities in the Army Reserve, call toll-free, 1-800-USA-ARMY.

ARMY RESERVE MEDICINE.
BE ALL YOU CAN BE.

CONTINUING MEDICAL EDUCATION

(Continued from Page 622)

February 5-9—**Sixth Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. Contact: (801) 379-7178.

February 10-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sat-Sat. The Yarrow, Park City. Contact: (801) 581-7480.

February 13-16—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Salt Lake Hilton, Salt Lake City. Contact: (801) 581-8635.

February 16-20—**Thirty-Fifth Annual Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: (801) 581-6115.

February 17-21—**Thirty-First Annual Ob/Gyn Update** (Sponsor: UUMC). Sat-Wed. The Yarrow, Park City. Contact: (801) 581-5501.

February 21-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Fri. Park City. Contact: (801) 584-1226.

February 21-24—**Teratology for the Practitioner** (Sponsor: UUMC). Wed-Sat. Park City. Contact: (801) 581-5501.

February 21-24—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott, Salt Lake City. Contact: (801) 521-1315.

March 3-10—**Advances in Internal Medicine** (Sponsor: UUMC). Sat-Sat. Snowbird. Contact: (801) 581-8664.

March 12-17—**Wilderness Medicine** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

May 3-4—**Ethics and Health** (Sponsor: UUMC). Thurs-Fri. University of Utah Health Science Center, Salt Lake City. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
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Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 4-5—**Pediatric Pain.** TBA. Thurs-Fri. Contact: U/W.

January 18—**Law & Medicine Symposium.** Tacoma. Thurs. Contact: PCMS, (206) 627-7137.

January 24-26—**Modern Molecular Biology for Physicians.** Seattle. Wed-Fri. Contact: U/W.

February 1-3—**Medical and Surgical Management of Heart Disease.** Seattle. Thurs-Sat. Contact: U/W.

February 2—**Peripheral Vascular Disease, 1990.** Seattle. Fri. Contact: VMMC.

February 8-9—**Cancer Review 1990.** Tacoma. Thurs-Fri. Contact: PCMS, (206) 627-7137.

COURSE SPONSORS AND CONTACT INFORMATION

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U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.
VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

February 8-10—**Ophthalmology: Annual President's Meeting.** Seattle. Thurs-Sat. Contact: (206) 441-9762.

February 9-10—**Cardiology Conference.** Seattle. Fri-Sat. Contact: VMMC.

February 28—**AIDS Update.** Tacoma. Wed. Contact: PCMS, (206) 627-7137.

March 3—**AIDS Issues '90.** Kirkland. Sat. Contact: Evergreen Hospital, (206) 823-7599.

March 8-9—**Tacoma Academy of Internal Medicine Annual Review.** Tacoma. Thurs-Fri. Contact: CME Pierce County.

March 9—**Risk and Insurance Management for Physicians in Practice.** Seattle. Fri. Contact: VMMC.

March 15-16—**Primary Care Orthopaedics.** Seattle. Thurs-Fri. Contact: U/W.

March 21-23—**Recent Advances in Cancer Detection.** Seattle. Wed-Fri. Contact: U/W.

March 26-April 6—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Sun. Contact: U/W.

March 29-31—**Trauma and the Elderly.** Seattle. Thurs-Sat. Contact: U/W.

April 6—**A Day of Infectious Disease.** Seattle. Fri. Contact: VMMC.

April 13-14—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: (206) 627-7137.

April 27—**Dermatology.** Tacoma. Fri. Contact: (206) 627-7137.

WYOMING

February 25-March 3—**Wyoming Academy of Family Physicians Annual Ski Meeting and Family Practice Update.** Jackson Hole. Sun-Sat. Contact: Hughes Planning, PO Box 3556, Jackson 83001: 1 (800) 342-7526.

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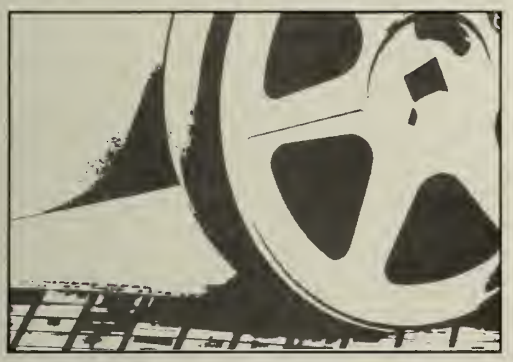

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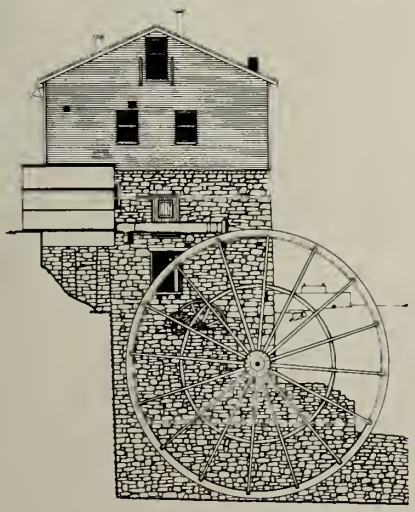

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Clinical Investigation

Thyroid Hormone Levels in the Acquired Immunodeficiency Syndrome (AIDS) or AIDS-Related Complex

WINSON W. TANG, MD, *San Diego, and* ELAINE M. KAPTEIN, MD, *Los Angeles*

Hypothalamic-pituitary dysfunction and thyroid gland cytomegalovirus inclusions have been described in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC). We evaluated 80 patients with AIDS or ARC for the frequency of hypothalamic-pituitary or thyroid gland failure and altered serum thyroid hormone levels due to nonthyroidal disorders. One patient had subclinical hypothyroidism. Of these patients, 60% had low free triiodothyronine (T_3) index values and 4% had low free thyroxine (T_4) indexes; none of the latter had hypothalamic-pituitary or thyroid gland failure, since all serum cortisol values were ≥552 nmol per liter (≥20 μg per dl) and all thyrotropin levels were ≤3 mU per liter (≤3 μU per ml), respectively. Those who died had lower total T_4 and T_3, free T_3 index, and albumin levels than those discharged from hospital. Serum total T_4 and T_3 levels correlated with albumin levels and total T_3 with serum sodium levels. Serum total T_3 levels best predicted the outcome of the hospital stay (accuracy = 82%). Thus, abnormal serum thyroid hormone levels in AIDS or ARC patients are most frequently due to nonthyroidal disorders, but hypothalamic-pituitary or thyroid gland failure may occur.

(Tang WW, Kaptein EM: Thyroid hormone levels in the acquired immunodeficiency syndrome [AIDS] or AIDS-related complex. West J Med 1989 Dec; 151:627-631)

Multiple endocrine abnormalities occur in patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC),[1-7] including hypothalamic dysfunction,[6,7] anterior pituitary insufficiency,[1-5] and adrenal or testicular failure.[2-6] At autopsy, pituitary lesions found include basophilic infiltration (22%), adenomas (15%), infarction (7%), and infection (1%).[8] In addition, cytomegalovirus (CMV) inclusions are present in the thyroid gland (14% to 71%), as well as in the adrenal (40% to 80%) and parathyroid glands (3%)[9-11] and in the testes.[11,12] These lesions of the hypothalamus, pituitary, and thyroid glands theoretically could result in an increased frequency of hypothyroidism in patients with AIDS or ARC. Because hypothyroidism may be overlooked clinically in severely ill patients, the diagnosis would depend on laboratory detection and confirmation.[13,14]

In the absence of hypothalamic-pituitary or thyroid gland failure, alterations of serum thyroid hormone levels due to nonthyroidal disorders would be expected to occur in patients with AIDS or ARC. These patients frequently have systemic infections, malignant neoplasms, and malnutrition—disorders known to be associated with reduced serum total triiodothyronine (T_3), free T_3 index, total thyroxine (T_4), and free T_4 index values in the absence of hypothyroidism.[15,16] The magnitude of changes in serum thyroid hormone values would be predicted to be related to the severity of illness in patients with AIDS or ARC, as reflected by the degree of malnutrition, the presence of hyponatremia,[5,17-19] and the outcome of the hospital stay.[15,20]

We studied 80 patients in hospital with AIDS or ARC to determine the frequency of altered serum thyroid hormone levels due to hypothyroidism or to nonthyroidal disorders and to evaluate the relationships of these alterations to the severity of nonthyroidal illness.

Materials and Methods

Serum thyroid hormone values were determined in 80 patients with AIDS or ARC admitted to the Internal Medicine service of the University of Southern California/Los Angeles County Medical Center between October 1 and December 31, 1986; of the 80, 6 men were admitted twice and had two sets of serum thyroid hormone levels done. All patients had serum total thyroxine, triiodothyronine uptake ratio, and serum thyrotropin (TSH) levels determined, and 50 patients had serum total triiodothyronine levels measured. All patients gave informed consent for inclusion into the study.

The study population consisted of 78 men and 2 women whose mean age was 36 ± 1 (standard error) years (range 19 to 60). The patients were white (46%), Hispanic (34%),

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Reprint requests to Elaine M. Kaptein, MD, Room 4250, Unit 1, University of Southern California School of Medicine, 1200 N State St, Los Angeles, CA 90033.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
CMV = cytomegalovirus
T_3 = triiodothyronine
T_4 = thyroxine
TRH = thyrotropin-releasing hormone
TSH = thyrotropin

black (19%), and Oriental (1%). The diagnosis of AIDS or ARC was based on the Centers for Disease Control criteria.[21,22] Patients had been diagnosed with AIDS or ARC for 4 ± 1 months before the current hospital stay. The risk factors for AIDS or ARC in the 78 men included 62 with homosexuality or bisexuality (80%), 5 with intravenous drug abuse (6%), 5 with both homosexuality and intravenous drug abuse, and 1 with blood transfusion; the other patients denied having any of the known risk factors. The two women had relationships with bisexual men. The diagnosis at the time of discharge or death after 18 ± 1 days in hospital included 79 with systemic infections (99%), 15 with malignant neoplasms (19%), and 8 with neurologic disease (10%).

Of these 80 patients, 68 (85%) has serum thyroid hormone levels measured to exclude hypothyroidism as a cause of hyponatremia, and the others had levels measured for other reasons. Hyponatremia was defined as a serum sodium concentration of less than 135 mmol per liter (< 135 mEq per liter) on two consecutive measurements (mean ± SE 127 ± 1 mmol per liter); the patients with normal serum sodium levels had a mean value of 137 mmol per liter (137 ± 1 mEq per liter). All patients were clinically euthyroid without symptoms or signs of hypothalamic-pituitary or adrenal insufficiency. Thyroid gland failure was defined as a serum thyrotropin level above 20 mU per liter or between 10 and 20 mU per liter in association with an exaggerated TSH response to thyrotropin-releasing hormone (TRH), with a normal or reduced free T_4 index.[13-16,23]

Serum biochemical values were measured using an autoanalyzer SMAC II (Technicon Instrument Corporation, Tarrytown, NY). Serum total T_4, total T_3, TSH, and T_3 uptake values were measured by commercial antibody-coated tube methods (ICN Micromedic Systems, Horsham, Pa). The T_3 uptake values were calculated as the antibody uptake of T_3 labeled with iodine 125 divided by the total ^{125}I-T_3 added to the specimen (bound/total); this method is most commonly used in clinical practice. The T_3 uptake values were also calculated by dividing the antibody uptake of the ^{125}I-T_3 by the residual serum protein-bound counts (bound/serum); this ratio corresponds much more closely to the predictions of the mass action law on which these procedures are based.[24] These T_3 uptake values were normalized to a ratio by using a pooled reference standard. The free T_4 index and free T_3 index values were calculated as the product of the total hormone concentration and the T_3 uptake ratio (bound/total or bound/serum).

Serum sodium and age were expressed as the mean ± standard error. Because the thyroid hormone values and albumin concentrations were better described by log distributions, logarithmic transformations were used for the purpose of analysis. Statistical differences between groups were evaluated using unpaired Student's *t* tests adjusted for variances or unpaired ranked-sum tests for data that were not normally distributed. Categoric variables were compared by the χ^2 or Fisher's exact test. The relationships between continuous variables were assessed by linear regression analysis. A *P* value less than .05 was considered to be significant. These computational analyses were carried out using the CLINFO computer package of the Clinical Research Center at the University of Southern California. Logistic regression analysis was used to model the probability of outcome as a function of risk factors, clinical characteristics, and therapeutic interventions[25] using the Statistical Analysis System on the IBM mainframe computer of the University of Southern California.

Results

The mean serum thyroid hormone values for the study population are presented in Tables 1 and 2. Because the mean bound/total and bound/serum values for the T_3 uptake ratio, free T_4 index, and free T_3 index were similar, only the bound/total values are provided in the text. The mean serum total T_4 value (94 nmol per liter [7.3 μg per dl]), T_3 uptake ratio (1.13), free T_4 index (8.3), and TSH value (1.7 mU per liter [μU per ml]) were within the laboratory reference range for the total population, while the mean serum total T_3 value (0.7 nmol per liter [47 ng per dl]) and free T_3 index (52) were below the laboratory reference range. Calculating the T_3 uptake ratio values as bound/serum instead of bound/total resulted in a significantly larger number of elevated values (57% versus 38%, $P < .02$). The number of patients with abnormal free T_4 or free T_3 indexes was not substantially changed, however, when calculated by the bound/serum compared with the bound/total method (free T_4 index: 2.3% versus 4.7%, and free T_3 index: 72.5% versus 75.0%, respectively).

There were three patients with free T_4 indexes below the lower normal reference range of 4.5, with values of 2.0, 3.7, and 4.1, respectively; their serum TSH values were 1.0, 1.0, and 2.3 mU per liter (μU per ml), and morning serum cortisol values were 541, 563, and 709 nmol per liter (19.6, 20.4, and 25.7 μg per dl), respectively; all three patients had normal or elevated blood glucose levels. One patient had a high free T_4 index of 13.8 and a serum free T_3 index of 67, without clinical evidence of hyperthyroidism. This patient had AIDS and died three days after admission—before a TRH stimulation test could be done. Of the 50 patients studied, 30 (60%) had free T_3 indexes below the normal reference range of 70, and 40 (80%) had values below 100. There were five patients with TSH values above the upper normal range of 5 mU per liter. In the four patients with TSH values ranging from 5.1 to 9.3 mU per liter (mean: 6.5 mU per liter), total T_4 and free T_4 index values were within the normal range (mean: 77.2 nmol per liter [6.0 μg per dl] and 7.0, real ranges: 57.9 to 114.5 nmol per liter [4.5 to 8.9 μg per dl] and 5.7 to 8.6, respectively), and were considered to be euthyroid.[23] The patient with the serum TSH value of 14.3 mU per liter had a total T_4 of 60.5 nmol per liter (4.7 μg per dl), a free T_4 index of 5.7, and an increase of the TSH from 11.7 to 39.1 mU per liter 30 minutes after receiving 250 μg of TRH intravenously; this patient was severely ill with *Pneumocystis carinii* pneumonia. These findings are compatible with subclinical hypothyroidism due to thyroid gland failure.[13,23]

Patients with AIDS did not differ significantly from those with ARC with respect to serum thyroid hormone levels (Tables 1 and 2). The mean serum albumin concentration,

TABLE 1.—*Serum Thyroid Hormone and Albumin Values* in Patients With the Acquired Immunodeficiency Syndrome (AIDS) or AIDS-Related Complex (ARC)*

Thyroid and Albumin Values	*Total Population (N=80)*	*AIDS Patients (N=66)*	*ARC Patients (N=14)*	*Hyponatremia*	*Normonatremia*	*Outcome: Died (N=23)*	*Outcome: Discharged (N=57)*	*Laboratory Range*
(Number of specimens)	(86)	(71)	(15)	(74)	(12)	(23)	(63)	
Total T_4, μg/dl	7.3†	7.4	7.1	7.1‡	9.0	6.3‡	7.8	4.5 -13.2
	5.0-10.7§	5.0 -11.0	5.4 - 9.4	4.8 -10.5	7.2 -11.2	3.8 -10.3	5.7 -10.6	
T_3 Uptake Ratio B/T	1.13†	1.14	1.11	1.16‖	1.00	1.23‖	1.10	0.88- 1.19
	0.99- 1.30§	0.99- 1.31	0.99- 1.25	1.02- 1.31	0.86- 1.16	1.08- 1.41	0.97- 1.24	
B/S	1.24†	1.25	1.20	1.28‖	1.02	1.44‖	1.18	
	0.99- 1.57§	0.99- 1.59	1.00- 1.45	1.04- 1.59	0.81- 1.28	1.13- 1.83	0.96- 1.44	
Free T_4 Index B/T	8.3†	8.4	7.9	8.2	9.0	7.8	8.5	4.5 -13.2
	6.1 -11.3§	6.1 -11.6	6.4 - 9.8	5.9 -11.4	7.5 -10.9	5.2 -11.6	6.5 -11.0	
B/S	9.1†	9.3	8.6	9.1	9.1	9.1	9.2	
	6.9 -12.1§	6.9 -12.4	7.0 -10.5	6.8 -12.2	7.4 -11.3	6.5 -12.7	7.1 -11.9	
TSH, μU/ml	1.7†	1.7	2.4	1.8	1.5	1.5	1.9	≤5.0
	1.0 - 3.1§	1.0 - 2.8	1.1 - 5.3	1.0 - 3.2	1.0 - 2.5	1.0 - 2.2	1.0 - 3.5	
Albumin, grams/dl	2.7†	2.6¶	3.0	2.6‖	3.4	2.2‖	2.9	3.9 - 5.0
	2.0 - 3.5§	1.9 - 3.5	2.6 - 3.5	2.0 - 3.3	2.8 - 4.0	1.7 - 2.9	2.3 - 3.6	

B/S=bound/serum, B/T=bound/total, T_3=triiodothyronine, T_4=thyroxine, TSH=thyrotropin

*To convert to SI units: for total T_4 value and free T_4 index (μg/dl), multiply by 12.87 to get nmol/liter; for TSH value (μU/ml), multiply by 1.00 to get mU/liter; for albumin value (grams/dl), multiply by 10 to get grams/liter.
†The numbers represent the geometric mean.
‡$P<.05$ comparing either the groups with AIDS with those with ARC, hyponatremia with normonatremia, or survivors with nonsurvivors.
§The numbers represent the antilogarithmic values of 1 standard deviation about the logarithmic mean.
‖$P<.001$ comparing either the groups with AIDS with those with ARC, hyponatremia with normonatremia, or survivors with nonsurvivors.
¶$P<.01$ comparing either the groups with AIDS with those with ARC, hyponatremia with normonatremia, or survivors with nonsurvivors.

TABLE 2.—*Serum Triiodothyronine (T_3) Values* in Patients With the Acquired Immunodeficiency Syndrome (AIDS) or AIDS-Related Complex (ARC)*

T_3 Values, ng/dl	*Total Population (N=80)*	*AIDS Patients (N=66)*	*ARC Patients (N=14)*	*Hyponatremia*	*Normonatremia*	*Outcome: Died (N=23)*	*Outcome: Discharged (N=57)*	*Laboratory Range, ng/dl*
(Number of specimens)	(50)	(43)	(7)	(43)	(7)	(10)	(40)	
Total T_3	47†	45	63	41‡	108	22‡	53	70-200
	21-105§	20-100	30-133	19-88	74-157	12-42	23-121	
Free T_3 Index B/T	52†	50	72	47‡	108	27‡	59	70-200
	26-106§	25-101	35-148	24-94	79-146	15-48	28-124	
B/S	57†	54	79	52‡	109	31‡	63	
	30-109§	29-103	39-159	27-98	80-149	18-54	31-128	

B/S=bound/serum, B/T=bound/total

*To convert total T_3 value and free T_3 index (ng/dl) to SI units, multiply by 0.01536 to get nmol/liter.
†The numbers represent the geometric mean.
‡$P<.01$ comparing either the groups with AIDS with those with ARC, hyponatremia with normonatremia, or survivors with nonsurvivors.
§The numbers represent the antilogarithmic values of 1 standard deviation about the logarithmic mean.

however, was lower in patients with AIDS (26 grams per liter [2.6 grams per dl]) than in those with ARC (34 grams per liter [3.4 grams per dl], $P<.005$).

Because hyponatremia may reflect the severity of illness in patients with AIDS or ARC[5,17-19] and alterations of serum thyroid hormone levels in euthyroid patients with nonthyroidal illnesses are related to the severity of illness,[15] serum thyroid hormone values from hyponatremic and normonatremic patients were compared (Tables 1 and 2). The mean serum total T_4, total T_3, and free T_3 index values of the hyponatremic group were lower than those of the normonatremic group, while free T_4 indexes did not differ significantly. The T_3 uptake ratios were higher in the hyponatremic group. Of the 74 hyponatremic patients, 21 (28%) died during their hospital stay, as did 2 of the 12 normonatremic patients (17%); this difference was not statistically significant.

In all, 23 patients died during their hospital stay, and the other 57 were discharged. There were no differences in age, duration of diagnosis of AIDS or ARC, or serum sodium concentrations between those who were discharged and those who died. Serum total T_4, total T_3, free T_3 index values, and albumin levels were significantly lower and T_3 uptake ratios higher, however, in those who died, while free T_4 indexes were not different. In addition, all 23 patients who died but only half of those who were discharged (28) had serum total T_3 levels below 1.08 nmol per liter (70 ng per dl, $P=.006$), and T_3 uptake ratios were elevated in 17 patients who died (74%) and 14 of those who were discharged (25%, $P<.001$).

There were positive correlations of concentrations of serum albumin with those of serum total T_4, total T_3, and sodium levels, and inverse correlations of concentrations of albumin with T_3 uptake ratio (Table 3). In addition, a significant direct relationship was present between total T_3 and serum sodium concentrations (Table 3). Finally, serum total T_4 levels correlated with serum total T_3 values ($r=.58$, $P<.001$).

TABLE 3.—*Correlations of Serum Thyroid Hormone Levels With Serum Albumin and Sodium Levels*

	Serum Albumin		Serum Sodium	
	r*	Equation†	r*	Equation†
Total thyroxine (T_4)	.60	$\ln T_4 = 1.19 + 0.83 \ln$ Albumin	.35	
Total T_3	.80	$\ln T_3 = 1.25 + 2.53 \ln$ Albumin	.58	$\ln T_3 = -8.39 + 0.095$ Sodium
T_3 uptake ratio (B/T)	−.67	$\ln T_3UR = 0.45 - 0.33 \ln$ Albumin	−.34	
T_3 uptake ratio (B/S)	−.68	$\ln T_3UR = 0.78 - 0.57 \ln$ Albumin	−.38	
Sodium	.44			

B/S=bound/serum, B/T=bound/total, ln=natural logarithm, T_3UR=triiodothyronine uptake ratio

*All *r* values are significant at the $P < .01$ level.
†Equations are given only for relationships with *r* values ≥ .50 and are given for metric units.

Using logistic regression analysis, the total T_3 measurement was the best prognostic indicator with an overall classification accuracy of 82%, with a 17.0% falsely abnormal (false-positive) rate (patients who were discharged but were predicted to die) and a 33.3% falsely normal (false-negative) rate (patients who died but were predicted to be discharged). Sensitivity was high, therefore, at 97.5%, and specificity was low at 20%. Serum albumin concentration, which was highly correlated with total T_3, was the next best predictor of outcome, with an overall classification accuracy of 76% and a 22% false-positive rate and a 42% false-negative rate. Sensitivity was also high at 92%, and specificity was low at 30%. Using the population means for serum total T_3 and albumin as arbitrary cutoff points, 39.1% of patients with a total T_3 value of 0.7 nmol per liter (47 ng per dl) or less and 3.7% with a value above 0.7 nmol per liter died ($P < .01$, sensitivity = 67.5%, specificity = 90%), and 46.2% with a serum albumin of 27 grams per liter (2.7 grams per dl) or less and 10.6% with a value above 27 grams per liter died ($P < .001$, sensitivity = 66%, specificity = 78%).

Discussion

Our findings indicate that serum thyroid hormone values are frequently altered in patients with AIDS or ARC and that these changes are most commonly due to the nonthyroidal illnesses and much less frequently to impaired hypothalamic-pituitary or thyroid gland function, as in other nonthyroidal illnesses.[15,16,26]

Although CMV inclusion bodies have been described in the thyroid gland,[9,11] overt thyroid gland failure was not found in patients previously studied or in our 80 patients with AIDS or ARC. One of our patients with AIDS, however, had subclinical hypothyroidism.[13,23] The cause of this patient's thyroid gland failure was not determined and may represent either a coincidental occurrence of hypothyroidism or may be due to an AIDS-related thyroid gland destruction. Thyroid gland failure occurs in 0.6% to 1.1% of the general population,[13,27,28] is twice as frequent in women as in men,[13] and is much more common in the elderly (4.4% to 5.9%).[28] Thus, the frequency of hypothyroidism in young men would be expected to be less than 0.5%. Our study population was too small to determine whether an increased prevalence of primary hypothyroidism was present in patients with AIDS or ARC. Further, although hypothalamic dysfunction[6,7] and pituitary failure are reported to occur in persons with AIDS or ARC,[1-6] none of our patients had hypothyroidism due to overt hypothalamic-pituitary failure, and only one case of central hypothyroidism due to toxoplasmosis is reported in the literature.[1] Thus, although hypothyroidism may occur secondary to hypothalamic-pituitary or thyroid gland lesions in patients with AIDS or ARC, requiring levothyroxine replacement therapy,[13] the frequency appears to be relatively low.

Reduced serum total T_3 levels and free T_3 indexes were the most frequent alterations observed in our euthyroid patients in hospital with AIDS or ARC. This is consistent with previously described patients with other nonthyroidal disorders including infections, malignant neoplasms, and malnutrition, where the earliest and most common alterations of serum thyroid hormone levels are decreased total and free T_3 concentrations resulting from a reduced peripheral conversion of T_4 to T_3.[15,16] These changes in T_3 metabolism are considered to be adaptive by minimizing protein breakdown, and patients with the low T_3 state of nonthyroidal illness have not been shown to benefit from thyroid hormone replacement therapy.[15,16] These findings also may be important to consider when treating patients infected with the human immunodeficiency virus.

Abnormalities of serum total T_4 levels were detected in six of our euthyroid patients and included increased as well as reduced total T_4 and free T_4 index values without clinical or biochemical evidence of hyperthyroidism or hypothyroidism. Elevated serum total T_4 and free T_4 index values have been noted to occur transiently in euthyroid patients with mild to moderate nonthyroidal illnesses and may be related to a reduced clearance of T_4 from the body rather than to an increased thyroid gland production of T_4.[15] Thus, these patients should be differentiated from those with hyperthyroidism to avoid unnecessary and potentially harmful therapy.[15,23]

The patients with reduced total T_4 and free T_4 index values had serum TSH levels below 10 mU per liter (μU per dl) and did not have clinical or biochemical evidence of overt hypopituitarism. These laboratory findings are compatible with the low total T_4 state of severe nonthyroidal illness, which is primarily due to a reduced binding of T_4 to serum carrier proteins rather than to decreased thyroid gland production of T_4[15,16,23] and does not require or benefit from levothyroxine therapy.[15,16] The minor elevations of serum TSH levels may be due to TSH, which is immunoactive but not bioactive.[15]

The recalculation of the T_3 uptake ratio, free T_4 index, and free T_3 index values by the bound/serum method significantly increased the number of high T_3 uptake ratios but did not significantly reduce the number of low free T_4 and free T_3 indexes. Thus, although theoretically the bound/serum method is a more accurate calculation of the T_3 uptake ratio,[24] it is not used frequently in clinical practice and may be of minimal benefit in screening persons with AIDS or ARC for the presence of thyroid dysfunction.

Serum total T_4, total T_3, and T_3 uptake ratio values in our patients admitted to hospital with AIDS or ARC were related to serum albumin and sodium concentrations, as well as to death during the hospital stay. Similar relationships of serum total T_4 and total T_3 levels with albumin concentrations have been reported in patients with other nonthyroidal disorders.[26] Serum albumin levels reflect the nutritional state,[29] and malnutrition and catabolism are known to decrease serum total T_3 and total T_4 levels.[15,16] Thus, these alterations may be causally related. The T_3 uptake ratios are inversely related to serum thyroxine-binding globulin concentrations,[13] and thyroxine-binding globulin, as well as albumin, is synthesized by the liver; thus, both measurements may reflect alterations in the visceral protein state in patients with AIDS or ARC. These alterations in nutritional variables may, in turn, be related to the severity of the illness.

Hyponatremia has been previously reported to relate to the severity of myocardial infarction,[17] and in patients with a variety of nonendocrine disorders may be an indicator rather than a cause of a poor prognosis and death.[18,19] Similarly, in patients with AIDS or ARC studied at our institution, death during a hospital stay was higher in those with hyponatremia (30%) than with normonatremia (16%).[5] Although the same trend was observed—28% versus 17%, respectively—in our group, the difference in mortality was not significant owing to the smaller population studied. The relationship between serum total T_3 and sodium levels in our study most likely indicates that hyponatremia and reduced serum total T_3 levels reflect the severity of the nonthyroidal illness; these alterations are unlikely to be causally related.

Serum total T_4 and total T_3 levels were lower and T_3 uptake ratios higher in patients with AIDS or ARC who died during their hospital stay, a finding similar to that in those who die of acute critical nonthyroidal illnesses.[20] In the latter group, serum total T_4 levels were better than the total T_3 values as predictors of survival during the hospital stay,[20] while in this study, serum total T_3 levels were better indicators. In the seriously ill patients described in 1982, 43% had reduced total T_4 and 68% had decreased total T_3 levels below the normal reference range, compared with 7% and 62%, respectively, in this study. The low frequency of reduced total T_4 levels in these patients with AIDS or ARC may account for its poor predictive ability. Because the serum total T_3 level appears to reflect the severity of malnutrition and nonthyroidal illness in in-hospital patients with AIDS or ARC, its measurement might prove useful in evaluating the efficacy of nonendocrine therapy.

Differentiating decreased total T_4 and free T_4 index values due to hypothalamic-pituitary or thyroid gland failure from reduced serum levels in euthyroid patients with nonthyroidal disorders is of clinical importance because hypothyroidism may contribute to morbidity and mortality if untreated and can be reversed by levothyroxine therapy.[13,14] On the other hand, patients with low total T_4 and free T_4 index values due to nonthyroidal disorders are clinically and biochemically euthyroid[15,16] and do not require thyroid hormone therapy. Indeed, administering thyroid hormones to euthyroid patients with nonthyroidal disorders has not been proved to be beneficial and may increase catabolism, as well as contributing to morbidity and mortality.[15,16] Consequently, the differentiation of hypothyroidism from alterations due to nonthyroidal disorders should be an integral part of the evaluation of patients with AIDS or ARC who have reduced free T_4 index values. Because hypothyroidism can be overlooked, particularly in patients with severe concurrent nonthyroidal illnesses,[13,14] the diagnosis depends on laboratory screening and confirmation.[23,30]

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Infection With the Human T-Lymphotropic Virus Type I

A Review for Clinicians

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The human T-cell lymphotropic virus type I (HTLV-I) is the first retrovirus identified in humans. It has been responsible for a number of clinical syndromes, most notably adult T-cell leukemia or lymphoma and tropical spastic paraparesis. In the United States, infection with this virus is most frequently found in specific subsets of our population, particularly in those who live in the southeastern states, have southern Japanese ancestry, or share intravenous drug paraphernalia. Understanding the epidemiology and clinical manifestations of this virus is necessary to properly diagnose and care for patients with HTLV-I infection.

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Although still uncommon in many parts of the United States, infection with the human T-cell lymphotropic virus type I (HTLV-I) has been identified in immigrants from endemic areas; blacks and Native Americans from the southeastern United States; and, with increasing frequency, in intravenous drug users. In Hawaii, antibodies to the virus and those diseases related to viral infection are found predominantly in the Japanese population and, in particular, in those whose ancestors immigrated from southern Japan. For physicians practicing among patients from these high-risk groups, HTLV-I infection and its associated disease states will present an increasing challenge. These physicians will not only need to be familiar with the virus and its associated diseases but will also be challenged with the responsibility of influencing the rate at which the virus spreads throughout the United States and the world.

We review the virus and the means by which it is spread and manifests disease states. In addition, we address several methods by which practicing physicians can influence the spread of this virus.

HTLV-I Virus

The HTLV-I virus was the first of several retroviruses identified in humans (Table 1). It was initially isolated in 1978 by Gallo and Poiesz from the T lymphocytes of a patient with a cutaneous T-cell lymphoma.[1,2] Since that time the virus has been associated etiologically with adult T-cell leukemia or lymphoma (ATL) but only occasionally with the malignant neoplasms from which it was first isolated.

The HTLV-I virus is a type C retrovirus. Being an RNA tumor virus, it depends on the enzyme reverse transcriptase for its replication. This enzyme uses the viral RNA as a template for the production of DNA, which then randomly integrates into the chromosomal DNA of the host cell. Once there, viral replication occurs by using the cell's own synthetic machinery, producing new virions containing viral RNA, as well as those proteins responsible for the packaging of these virions (Figure 1).

The clinical course of HTLV-I infection is related predominantly to its effects on the T lymphocyte. The virus preferentially attacks the $CD4^+$ or helper T lymphocyte. Once inside a T cell, the provirus is randomly integrated into the cellular genome. Thus, polyclonal proviral integration is found in peripheral blood lymphocytes. When progression to ATL occurs, the virus is found only in a monoclonal pattern (Figure 2).

The location of the monoclonal HTLV-I provirus integration is different for each patient with ATL. It does not appear that HTLV-I provirus need be present in a single location for it to be leukemogenic, as occurs with other viruses with the potential to create malignant disorders. Its capacity for leukemogenesis is thought to be related to the presence of a gene, called *tax* (analogous to the human immunodeficiency virus's *tat*) for transactivation factor, within the viral genome. The *tax* gene appears to induce the production of interleukin-2 and its receptors and may therefore initiate abnormally rapid autologous cellular growth (Figure 3).

Recent work has shown that cell lines containing *tax* are able to be passed from generation to generation in mice and have the ability to convey malignant potential in these mice and their offspring.[3,4] Of interest is that these mice developed tumors that closely resembled those seen in neurofibromatosis.[4] One group has reported malignant fibrous histiocytoma, a mesenchymal tumor not dissimilar to those found in neurofibromatosis, developing in a patient with HTLV-I.[5] We suspect that more cases of HTLV-I-associated mesenchymal tumors soon may be reported in the medical literature.

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ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia or lymphoma
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
HTLV-I = human T-cell lymphotropic virus type I

TABLE 1.—*Human Retroviruses and Their Associated Clinical Syndromes*

Virus	*Associated Syndrome*
Human T-lymphotropic virus type I	Adult T-cell leukemia; tropical spastic paraparesis
Human T-lymphotropic virus type II	Morphologic hairy cell leukemia; cutaneous T-cell malignant neoplasms
Human immunodeficiency virus type I	Acquired immunodeficiency syndrome
Human immunodeficiency virus type II	Acquired immunodeficiency syndrome

Epidemiology

Human T-cell lymphotropic virus type I is endemic in numerous parts of the world. In the continental United States, it is most common in blacks and Native Americans from the southeastern states. In a small survey of healthy blacks from Georgia, the prevalence of HTLV-I antibodies was 2.1%.[6] In Hawaii, HTLV-I seropositivity is found in 20% of immigrants from southern Japan and their offspring but seldom in the white, Chinese, Filipino, or Pacific Islander population.[7,8] It may be expected, however, that with both the increasing frequency of intermarriage among ethnic groups and the increased mobility of our society, we will soon be seeing seropositivity in a broader spectrum of our population.

Several other areas are endemic for HTLV-I: southern Japan, the Caribbean islands, South America, and Africa. Less commonly reported sites include Israel, Taiwan, New Guinea, southern Italy, and the Arctic. Case reports of ATL also have originated from numerous nonendemic locations, although many of these reports involved patients who had immigrated from locations known to be endemic for HTLV-I.

More recently, investigators have found HTLV-I in the intravenous drug user population within the United States, with a prevalence of HTLV-I antibodies reported to range from 7% to 49%.[9-11] Notably, a number of these patients may be coinfected with human immunodeficiency virus (HIV). Whether infection with both agents produces a more aggressive clinical course remains unknown.

Infection with HTLV-I is thought to have occurred first in Africa and then spread to other endemic regions through commercial and slave trading.[12] Further spread has occurred with immigrants and foreign visitors.[13,14] In Hawaii, the virus is thought to have arrived with immigrants from southern Japan.[7,8] While current estimates are that more than a million residents in Japan may be infected with HTLV-I,[15,16] the overall prevalence of seropositivity in the United States is much lower. A blood bank study found that 0.025% of random blood donors in the United States were seropositive for HTLV-I.[17] Using 1988 estimates for the US population,[18] it may be projected that approximately 62,000 Americans are seropositive.

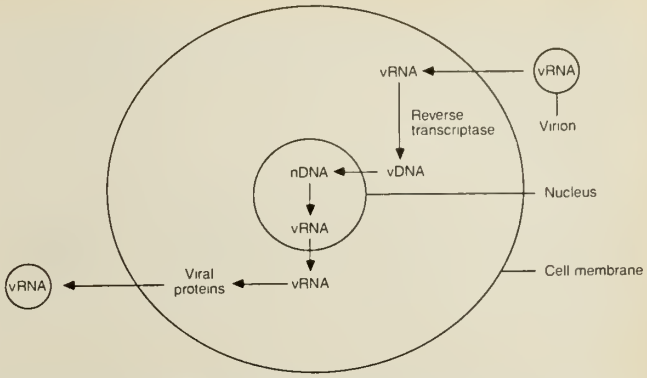

Figure 1.—The life cycle of the HTLV-I virus is shown. nDNA = host nuclear DNA, vDNA = viral DNA, vRNA = viral RNA

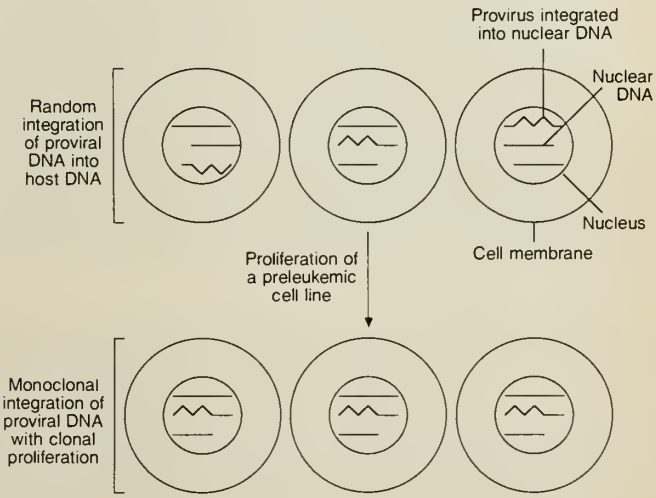

Figure 2.—The schematic shows the progression from polyclonal to monoclonal integration of proviral DNA.

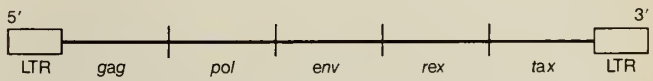

Figure 3.—The HTLV-I proviral genome is shown schematically.

The long terminal repeat (LTR) influences viral transcription, integration, and expression; *gag* encodes for viral core antigens and structural proteins; *pol* encodes for reverse transcriptase; *env* encodes for envelope glycoproteins; *rex* encodes for proteins that regulate *gag* protein synthesis; and *tax* (transactivation factor) encodes for several proteins that can activate distant cellular genes and may also modulate the production of interleukin-2 and its receptor.

Transmission

Several modes of transmission for the HTLV-I virus exist. Vertical transmission from mother to child at birth and transplacental transmission are thought to occur. Sexual intercourse is also a mode of transmission, although seronegativity in spouses of seropositive persons suggests that it is a relatively inefficient means of transmission. These modes account for the often-seen familial clustering of HTLV-I infection.

Breast milk from mothers who are HTLV-I seropositive has been shown to contain HTLV-I-infected lymphocytes.[19] The number of HTLV-I-infected cells in both breast milk and the mother's peripheral blood has been found to correlate with the risk of infection to the breast-feeding child.[20] As

expected, infants born to seropositive mothers and bottle-fed are considerably less likely to display HTLV-I antibodies at the age of 12 months than those who were breast-fed.[21] Breast-feeding is likely the most common mode of transmission of the HTLV-I virus.

Seroconversion can also be found among recipients of cell-containing blood products—erythrocytes, platelets, and leukocyte preparations—from infected donors.[22-25] Seroconversion rates have been reported to be as high as 63%.[22,24] Although no case of transfusion-acquired ATL has yet been reported, a rare progression to tropical spastic paraparesis has been described among recipients of infected blood.

Although the transmission of HTLV-I by insect or parasite vectors has been suggested, insufficient data are available to prove this.[26,27] This mode of transmission continues to be entertained both because of the high overall prevalence of HTLV-I in some endemic areas and because of the higher rates of antibody-positivity encountered with increasing age.

As noted earlier, transmission by contaminated drug paraphernalia occurs in intravenous drug users.[9-11] Because of their unreliability, intravenous drug users represent the greatest risk to our population as a whole. The prevalence of HTLV-I seropositivity may be as high as 47% in these persons,[11] although some of the data may be obscured by the cross-reactivity of HTLV-II in the HTLV-I enzyme-linked immunosorbent assay (ELISA).

Clinical Manifestations

A number of diseases have been associated with HTLV-I infection (Table 2). The most severe of these is acute adult T-cell leukemia or lymphoma. These patients usually have weight loss, lymphadenopathy, hepatosplenomegaly, and, occasionally, lytic bone lesions. Skin lesions from infiltration with leukemic cells may also be seen. The peripheral blood of patients with ATL usually shows leukocytosis with multilobulated lymphocytes. Hypercalcemia is common, and some patients will also have elevated serum bilirubin and lactate dehydrogenase values.[28]

Other patients may have clinical findings more similar to those of non-Hodgkin's lymphoma.[29] The biopsy specimens from these patients will have monoclonal integration of HTLV-I proviral DNA.[28]

A chronic, less symptomatic form of ATL has also been reported. Variably called smoldering or chronic ATL, this form has a fewer number of circulating leukemic cells and often diffuse lymphadenopathy.[28] Although this form of ATL usually follows a more indolent course, these patients must be observed for a progression to acute ATL, with its more aggressive clinical course.

Lastly, a preleukemic state (pre-ATL) has been reported.[30] Patients with this condition are asymptomatic but usually have oligoclonally integrated HTLV-I.[30] About half will develop either smoldering or acute ATL, while the others will remain in a carrier state.[28]

Researchers differ in their estimates as to how often HTLV-I infection will eventually develop into acute ATL. Studies in Japan suggest a lifetime risk of approximately 2%,[31,32] while in the Caribbean the risk before the age of 20 has been estimated to be about 4%.[33] Still other investigators suggest rates of less than 1%.[34,35] When a progression to symptomatic disease does occur, however, it is usually after a latent period lasting many years.

In the past, little therapy has proved beneficial for patients with the acute form of ATL. Neither the leukemic nor the lymphomatous forms of acute ATL respond well to conventional chemotherapy. Recently, however, two groups have reported complete and partial responses to several forms of interferon.[36,37] Whether this will become the treatment of choice in the future awaits clinical trials.

As is evident, HTLV-I infection will never develop into ATL in most patients. They are at risk, however, for several neurologic diseases, including tropical spastic paraparesis, also called HTLV-I associated myelopathy. This is a progressive myelopathy, with patients usually having weakness and sensory findings in the lower extremities and, when the disease is in an advanced stage, urinary incontinence. Spasticity is also a prominent finding in this syndrome. It has a broad age distribution, with a peak occurrence between 40 and 49 years, and appears to be more common in women than in men.[38] Although most often seen in Japan or the Caribbean, cases of tropical spastic paraparesis have also been reported in several locations in the United States (P.S.D.; A.J. Bodner, PhD; M. Okihiro, MD; and colleagues, "HTLV-I and Tropical Spastic Paraparesis in Hawaii," unpublished data, June 1989).[39] Antibodies to HTLV-I have been found in both the serum and cerebrospinal fluid of some patients with this disease.[39-41] Although this is characteristically a progressive, debilitating disease, recent studies have shown patients having symptomatic improvements following a short course of plasmapheresis[42] or corticosteroid therapy.[43]

Additionally, several investigators have suggested an association between HTLV-I and multiple sclerosis; this finding, however, has not been confirmed in subsequent investigations.[44-47] With the use of sophisticated DNA amplification techniques, parts of the viral genome can be detected in some patients with multiple sclerosis, but the significance of these signals is not known. In Jamaica, investigators found HTLV-I antibodies in six patients with an inflammatory polymyositis.[48]

As may be obvious from this discussion, HTLV-I, like

TABLE 2.—*Clinical Syndromes That May Be Associated With Human T-Cell Lymphotropic Virus Type I (HTLV-I) Infection*

Malignant Neoplasms	Neurologic Syndromes	Parasitic Diseases
Adult T-cell leukemia or lymphoma (ATL)	Tropical spastic paraparesis (HTLV-I-associated myelopathy)	Strongyloidiasis
Acute ATL	Mononeuritis	Filariasis
Chronic (smoldering) ATL	Inflammatory polymyositis	Malaria
Others postulated	Others postulated	Others
B-cell chronic lymphocytic leukemia	Multiple sclerosis	Thrombotic thrombocytopenic purpura
Sézary syndrome	Neurofibromatosis	Pulmonary alveolitis
Mycosis fungoides		Chronic inflammatory arthropathy
T-cell non-Hodgkin's lymphoma		Vasculitis
Mesenchymal tumors (?)		

HIV, appears to have a predilection for causing disease of the central nervous system. Although not understood well at this time, this might be either related to direct infection of the neuronal cells or secondary to the immunologic responses to viral infection.

Parasitic diseases, including strongyloidiasis, filariasis, and malaria, have been reported in patients with both asymptomatic HTLV-I carrier states and ATL. All have been suggested as possible cofactors that may affect the clinical course of HTLV-I infection.[28]

Of these parasites, the most extensively studied is strongyloidiasis. Investigators in Japan have reported a higher incidence of HTLV-I antibodies in patients with strongyloidiasis.[49] In Hawaii, an area not endemic for *Strongyloides stercoralis,* we, too, have found both ATL and HTLV-I seropositivity in several patients with strongyloidiasis.[50] In Okinawa, Nakada and colleagues have noted monoclonal integration of HTLV-I more frequently in patients with strongyloidiasis than in those without.[51] This has led them to suggest that *Strongyloides stercoralis* may play a role in the leukemogenesis of this virus.[51] Whether this in fact occurs remains unknown.

We have recently reported a case of thrombotic thrombocytopenic purpura in a patient seropositive for HTLV-I.[52] While there have been several reports of this disease in patients with HIV infection,[53-56] it had not previously been associated with HTLV-I. Additional studies will be needed before any conclusive association between these two disorders can be established, however.

It appears likely that other clinical conditions resulting from infection with HTLV-I will be reported as our experience with this virus becomes more widespread. Unfortunately, at the current time no treatment is available for those with asymptomatic infections. Consequently, the knowledge of a person's antibody status is only helpful from a preventive point of view. Perhaps in the future drugs such as azidothymidine, used for the treatment of patients infected with HIV, will be found useful for treating HTLV-I infection. Early studies suggest some in vitro activity of this drug and others against HTLV-I.[57,58] Clearly, preventing the spread of the HTLV-I virus is one area where we currently can make the greatest contribution to reducing the risks of this infection.

Preventive Measures

At the present time the burden of responsibility for treating and preventing HTLV-I infection and its associated clinical syndromes lies with those who care for patients from the populations at risk for acquiring this infection. In the United States this includes all who live in the southeastern states; those with southern Japanese ancestry; immigrants from Africa, the Caribbean islands, Japan, and Central and South America; and intravenous drug users who share needles. In addition, the spouses, children, and families of patients from these groups are at risk for acquiring HTLV-I infection. As one can immediately see, a large part of the American population may be at risk for exposure to HTLV-I.

Several approaches can be used to reduce the rate at which HTLV-I is spread (Table 3). Many of these hinge on first discerning those persons who are already infected. Several methods currently exist (Table 4). An ELISA assay, which is both sensitive and specific, was approved by the Food and Drug Administration in 1988 and is in routine use for screening donor blood for HTLV-I antibodies.[38] This step may be expected to reduce substantially the prevalence of transfusion-acquired HTLV-I infection, particularly in endemic locations.

TABLE 3.—*Methods That Could Be Employed to Reduce Transmission of Human T-Cell Lymphotropic Virus Type I*

Means of Transmission	*Method of Prevention*
Blood transfusion	Screening of donor blood supply
Childbirth	Screening of mothers at risk and discouraging them from breast-feeding
Sexual intercourse	Using condoms
Intravenous drug paraphernalia	Discouraging the sharing of needles and identifying seropositive drug users

TABLE 4.—*Tests Available for Identifying Human T-Cell Lymphotropic Virus Type I (HTLV-I) Viral Infection*

Test	*Comment*
ELISA (enzyme-linked immunosorbent assay)*	Rapid screening test; inexpensive; cannot distinguish HTLV-I from HTLV-II
RIA (radioimmunologic assay)	Confirmatory
Western blot	Confirmatory
Polymerase chain reaction	Confirmatory; minimal tissue needed, but subject to contamination
Virus culture	Difficult; time-consuming; expensive

*Currently used for the screening of the blood supply in the United States.

Although confirmatory tests for HTLV-I exist, they have not yet been approved by the Food and Drug Administration. When they become readily available, both the Western blot assay and the polymerase chain reaction[59,60] will be useful confirmatory tests.

Despite the lack of therapy for HTLV-I infection, the knowledge of a patient's antibody status could be used to substantially reduce the rate of spread of this virus. Mothers who test positive for HTLV-I should be instructed not to breast-feed their infants. The use of condoms can be expected to reduce the spread of virus among persons engaging in sexual intercourse with an infected partner. The sharing of needles should be discouraged among intravenous drug users, to prevent not only HTLV-I but also infection with HIV and the hepatitis B virus.

Increasing attention has been given to the use of autologous transfusion because HIV infection has entered the realm of transfusion-associated diseases. Autologous transfusions can reduce the rates of multiple infectious processes, including HTLV-I, HIV, hepatitis B, non-A, non-B hepatitis, and cytomegalovirus, as well as some noninfectious processes such as transfusion reactions. The use of autologous transfusions should be encouraged and programs should be instituted in centers where this procedure is not already being done. The effect of these programs on the transmission of HTLV-I will likely be small, however, now that routine screening for antibody in the donor blood supply has commenced.

Future Efforts

An improved understanding of the HTLV-I virus is necessary before we will be able to substantially alter its course in humans. The mechanisms of leukemogenesis, determi-

nants of viral latency and activation, and the process by which neurologic dysfunction is induced all are important areas of research. Ongoing studies include efforts to delineate how the *tax* gene promotes rapid cellular growth and what role this plays in the progression from an asymptomatic carrier state to overt ATL or tropical spastic paraparesis. Investigators also are looking for a method to follow proviral integration from a polyclonal state to monoclonality and, therefore, to ATL. This capability would allow earlier and possibly more effective therapy for this aggressive disease.

Clinical studies are also sorely needed. A thorough knowledge of the natural history of viral infection will be necessary to help guide subsequent therapeutic trials. These likely will include pharmacotherapy with drugs such as azidothymidine or the interferons for ATL, and corticosteroids or plasmapheresis for tropical spastic paraparesis.

Although a number of diseases have already been related to the HTLV-I virus, physicians in endemic locations should be looking for as-yet-unknown processes that may also be related to this virus. Diseases such as the vasculitides and peripheral nerve palsies are possibilities.

Rapid, inexpensive, and accurate assays for HTLV-I will need to be developed and made accessible to clinicians. Although the currently available ELISA assay is both rapid and inexpensive, concern exists that it may not adequately differentiate HTLV-I from HTLV-II. The extent to which HTLV-II has been masquerading as HTLV-I in previous studies is therefore unknown.

Lastly, as with HIV, our ultimate goal will continue to be to produce a safe and effective vaccine to prevent an initial infection with this virus. The highly conserved and stable nature of HTLV-I may make a vaccine a more achievable goal and therefore may serve as a model for developing an HIV vaccine.

Conclusion

By a concerted effort from those physicians who care for patients in the groups at high risk for HTLV-I infection and those involved in basic scientific research, it is hoped that a rapid resolution to the increasing prevalence of HTLV-I infection in the United States can be achieved. The greatest reservoirs remain those groups in whom the virus is endemic. Preventing transmission by these groups—most importantly to their offspring—remains our greatest opportunity to reduce the spread of this virus. The recent institution of HTLV-I antibody screening in donated blood should help somewhat. Ongoing efforts to educate physicians and patients about this disease should have a notable effect on preventing HTLV-I infection and its concomitant diseases.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Clinical Imaging—An Introduction to the Role of Imaging in Clinical Practice

Edited by Matthew Freedman, MD, Associate Professor of Diagnostic Radiology, Georgetown University School of Medicine; Associate Professor of Diagnostic Radiology, Johns Hopkins University School of Medicine; and Associate Professor of Diagnostic Radiology and Assistant Professor of Orthopedic Surgery, University of Maryland School of Medicine, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1988. 589 pages, $45.

This book is intended for use as the text in a three- to five-week radiology clinical clerkship course. The text begins with a chapter that discusses methods for analyzing imaging studies. In chapters 2 through 6 methods used for imaging the body are discussed. Chapters 7 through 62 cover the clinical applications of the imaging methods, divided by anatomic region, and the final chapter outlines medical economics and the effect of diagnostic imaging on the cost of health care.

The book is printed on good quality, 8½ × 11 paper with a large print size. Many pages are blank or have only a few lines of print.

Although the image quality of some of the illustrations is excellent, that is, unfortunately, not a uniform characteristic of the text. Many of the chest images, for example, are reproduced too dark, so that pulmonary vessels are not distinct. Most of the ultrasound and computed tomographic images are not of the high quality that is obtainable with state-of-the-art technology. Very few magnetic resonance (MR) images are included, with only a few MR images of the brain or spinal cord, areas in which MR has revolutionized our diagnostic ability. When MR images are shown, there is not an explanation of T1 and T2 relaxation values, something a medical student might be expected to know. Some of the captions of the illustrations are inadequate in that they fail to give the diagnosis or they refer the reader to the text. There are no color illustrations of Doppler or of gross or microscopic pathology for correlation, as there are in Lucy Squires's textbook for medical students. Several important entities are not discussed at all or are mentioned only in passing: Wilms's tumor, neuroblastoma, osteogenic sarcoma, leukemia, congenital heart disease, and congenital dislocation of the hip.

Aside from these deficiencies, however, there is much in the book to make it valuable to medical students. Specifically, I found the organization of each chapter to be attractive and practical. The key concepts are presented, the objectives are enumerated, the entity is discussed and illustrated, the findings are summarized, review questions are provided, a vocabulary of new words is listed, and, finally, there are suggestions for further reading.

I think that medical students will find that this book is a very palatable introduction to clinical radiology. The interested student will use this book as a stepping stone to read, in depth, other current radiology textbooks oriented either toward organ systems or new imaging technologies.

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Medical Progress

Bone Marrow Transplantation
Part I—Allogeneic

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Major progress in experimental and clinical research has made allogeneic bone marrow transplantation a highly effective therapy for a variety of malignant and nonmalignant diseases. Allogeneic bone marrow transplantation from histocompatible donors is now the therapy of choice for some of these disorders. We review in part I the history, technical approach, complications, and the results achievable with this therapeutic approach. Further experimentation and future goals are also discussed.

(Chao NJ, Blume KG: Bone marrow transplantation. Part I—Allogeneic. West J Med 1989 Dec; 151:638-643)

Bone marrow transplantation has evolved over the past 20 years to an acceptable and "first-line" therapy for certain diseases. This evolution paralleled the description of the human leukocyte antigen system, the development of intensive support systems such as broad-spectrum antibiotics, total parenteral nutrition, and transfusional support with platelets. Furthermore, understanding some of the immunologic aspects involved has helped in controlling distinct facets of transplantation such as graft-versus-host reaction.

The first documented description of bone marrow transplantation was made in 1939, when a woman with gold-induced aplasia was given marrow intravenously from a brother with identical blood group antigens.[1] Engraftment did not take place, and the patient died five days later. The modern era of transplantation began in the 1950s when experiments in animals suggested that mice could be protected from lethal irradiation by an infusion of bone marrow cells and, specifically, the regenerating marrow could be of donor origin.[2,3] Pioneer work by Thomas and co-workers at Seattle showed prolonged disease-free survival in a notable number of patients, even though they generally had relapsed advanced leukemias or multiply transfused aplastic anemia.[4] After these encouraging results, bone marrow transplantation was applied earlier for various diseases rather than in patients with end-stage disease, and results have improved consistently.

Most of the active therapies for malignant diseases are limited by bone marrow toxicity. This limitation can restrict the dosing and scheduling of potentially curative drug combinations. Thus, bone marrow transplantation provides a method where dose escalation can occur and where other physiologic toxicities limit the dose intensity. Higher drug dosing can result, then, in higher tumor cell kill, and, it is hoped, more cures. Finally, a bone marrow graft is a form of adoptive transfer where immunomodulation from the grafted tissue can be clinically significant, as is the case with graft-versus-leukemia effect.[5,6]

Technical Approach

Allogeneic bone marrow transplantation is the grafting of bone marrow from a donor into a recipient who is not an identical twin. At this time most transplants are of donor-recipient pairs who are matched for the HLA loci of the major histocompatibility complex. The chance of an HLA-identical donor-recipient pair being found among siblings is one in four. As the registry for unrelated donors grows, other unrelated persons who match at the HLA region may become donors. Long-term follow-up results and large numbers of patients have not been accumulated in the unrelated donor group, however.

Allogeneic transplantation can be used successfully for all the nononcologic disorders listed in Table 1 and for selected malignant diseases where a match can be found and where it is clinically indicated.

Before patients receive a graft, their endogenous bone marrow must be removed and their immune system suppressed. Immunosuppression is achieved with high doses of chemotherapy—usually accompanied by total body irradiation. Toxicities of the preparative regimen vary, depending on the agents used. Most agents cause notable mucositis, nausea, and vomiting. Other toxic effects include sterility, cataract formation, pulmonary fibrosis, hepatic and renal injury, cardiomyopathy, hemorrhagic cystitis, and neurotoxicity—tremors, seizures. Occasionally these can be fatal.

Once myeloablation and immunosuppression are completed, the recipient is ready to receive the bone marrow graft. The donor is taken to the operating room, and, with the patient under general or spinal anesthesia, the marrow is aspirated from the iliac crests. Particulate matter—bone spicules, fat, or small clots—is removed through a metal screen mesh.[7] The bone marrow is then infused intravenously into the recipient. In cases where there is a major ABO blood group mismatch, incompatible erythrocytes or the circulating isohemagglutinin in the host must be removed. This can be done through sedimentation with dex-

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This is part 1 of a two-part article. Part II will be published in the next issue of the *Western Journal of Medicine.*

ABBREVIATIONS USED IN TEXT

CML = chronic myelogenous leukemia
CMV = cytomegalovirus
Ph = Philadelphia [chromosome]

trans, differential centrifugation, ABO immunoabsorption of blood group antigens, or total plasma exchange.[8-10] The infused bone marrow, with its stem cells, migrates throughout the body and establishes itself in the bone marrow cavity and elsewhere, such as the Kupffer's cells in the liver, the microglia of the brain, and the macrophages in the lung.[11,12] The period of aplasia lasts about three weeks before enough newly formed leukocytes can be seen in the peripheral blood. During this period, the recipient is in danger of serious bleeding and sepsis from bacterial and fungal infections. Patients are frequently unable to eat or drink because of substantial mucositis. As the bone marrow engrafts and regenerates, the risk of acute graft-versus-host disease is at its peak.

Prophylactic measures are taken to minimize the occurrence of these complications. Red cells and platelets are transfused prophylactically or therapeutically, as necessary. Gut decontaminants are used to reduce endogenous flora. Broad-spectrum antibiotics are given to patients who have fever. If defervescence does not occur promptly, antifungal therapy such as amphotericin B is given. Cytomegalovirus (CMV) is another pathogen of concern because of the high mortality it can cause if pneumonia develops.[13-16] High-titer anti-CMV immunoglobulins may be used, and patients need to be monitored closely both clinically and radiographically for any pulmonary symptoms. Total parenteral nutrition is also frequently and effectively used to meet the increased caloric demands as a result of the therapy.[17,18] Finally, graft-versus-host reaction should be prevented, again because of the severe morbidity and possible death. The graft-versus-host reaction may be prevented by combinations of prednisone, cyclosporine, and methotrexate sodium.[19-21] Ongoing clinical studies should determine the best prophylaxis for cytomegalovirus and graft-versus-host reaction.

Complications

There are three major problems associated with allogeneic bone marrow transplantation. As previously mentioned, graft-versus-host reaction creates a serious barrier to effective transplantation. The graft-versus-host reaction can lead to graft-versus-host disease, which occurs as an acute reaction—arbitrarily defined as occurring within the first 100 days and associated with skin, gut, and liver dysfunction,[22] or as a chronic reaction that occurs after the first 100 days as a syndrome resembling various autoimmune phenomena.[23-29] Although the recipient and donor are matched at the HLA loci and intensive immunosuppression is used, the incidence of graft-versus-host disease varies from 26% to 76%, with an average of approximately 30%.[22,30-32] This can result in substantial morbidity and mortality—as much as 50%. Both forms of graft-versus-host disease can cause direct morbid effects, such as gastrointestinal bleeding, and death or increased morbidity and mortality from its treatment, resulting in an increased incidence of opportunistic infection.[33-35]

Efforts to understand and prevent graft-versus-host disease are a large fraction of allogeneic bone marrow transplant research. Permutations of combinations of methotrexate, cyclosporine, and prednisone are part of ongoing clinical trials. Promising results are being reported for a variety of T-cell depletion techniques.[36-40] Whether the lower incidence of graft-versus-host disease will result in improved survival rates is unclear. There are drawbacks to T-cell depletion, such as graft failure or higher relapse rates, which may negate the benefits of a lower incidence of graft-versus-host disease.[41-44] These data will become available as current studies mature. Preventing graft-versus-host disease will be of greater importance, especially with the increase in the number of unrelated donor transplants.

TABLE 1.—*Disorders and Clinical Conditions in Which Allogeneic Bone Marrow Transplantation Has Been Used Successfully*

Acute leukemia, de novo and secondary	Severe hemoglobin abnormalities
Chronic granulocytic leukemia	Congenital pure red cell aplasia
Acute "malignant" myelosclerosis	Paroxysmal nocturnal hemoglobinuria
Myelodysplastic syndromes	Severe combined immunodeficiency
Non-Hodgkin's lymphoma*	Osteopetrosis
Hodgkin's disease*	Wiskott-Aldrich syndrome
Multiple myeloma	Congenital leukocyte dysfunction syndromes
Hairy-cell leukemia	Hereditary storage disorders
Aplastic anemia	Glanzmann's disease
Thalassemia major	
Fanconi's anemia	

*Most centers use autologous bone marrow transplants.

A second obstacle in bone marrow transplantation is opportunistic infections. The most prominent example is interstitial pneumonia, caused by cytomegalovirus. Before current treatment regimens were developed, the mortality from CMV interstitial pneumonia approached almost 90%, affecting approximately 15% to 20% of allogeneic transplant patients.[14,34] Recently, notable strides have been made in the therapy for this disease. The use of the antiviral agent DHPG:9-(1,3-dihydroxy-2-propymethyl)guanine, or ganciclovir, in combination with high-titer anti-CMV immunoglobulin G has resulted in substantial improvement in survival rates—approximately 50% to 70%.[45-47] There is great interest in using these agents in the prophylaxis of CMV pneumonias.

Finally, leukemic relapse remains a major obstacle. New combinations of active agents have been developed. Traditionally, the conditioning regimen has consisted of total body irradiation and administering of cyclophosphamide.[48,49] Newer regimens replace a single-fraction total body irradiation with fractionated applications and substitute etoposide (VP-16-213) for cyclophosphamide.[50] Other regimens do not use radiation, employing instead a two-drug combination such as busulfan and cyclophosphamide.[19,51] As the toxicities of each high-dose agent become better understood, such combinations may lead to a lower incidence of relapse and potentially less host organ damage. Methods to control graft-versus-host disease without affecting a beneficial graft-versus-leukemia effect may have a positive effect in preventing leukemic relapse following transplantation.[52,53]

Results

What, then, are the results of such cost- and labor-intensive procedures? Overall, bone marrow transplants offer the hope of true cures to a large number of patients. Although cures are measured only as survival on Kaplan-Meier

curves, equally important is the quality of life for these patients following transplant. Only recently has attention been focused on this issue. A study of 203 patients at the City of Hope National Medical Center (Duarte, California) and Stanford University Medical Center (Stanford, California), with a median follow-up period of 3.6 years, reveals that more than 80% of patients graded their quality of life greater than 8 on a scale of 1 to 10, with 10 being the best. Their overall Karnofsky score was greater than 80%.[54] Data such as these document the favorable outcome for patients following allogeneic bone marrow transplantation.

Acute Lymphoblastic Leukemia

Allogeneic bone marrow transplantation has been done for all remission and relapse states in acute lymphoblastic leukemia. Clearly, as for any therapeutic modality, the variation in response rates is directly related to the disease status of the patients. For adult patients in their first complete remission, allogeneic bone marrow transplantation has been carried out successfully, with an actual survival rate of 63% after two to eight years.[55,56] Intensive chemotherapy without bone marrow transplant also results in significant actuarial disease-free survival and, presumably, cures.[57-59] This disease-free survival is more common in the pediatric population.[60] Randomized studies are necessary to establish whether adult patients with acute lymphoblastic leukemia and histocompatible marrow donors should receive allogeneic bone marrow transplants while in first complete remission rather than continued chemotherapy, with transplantation of those who relapse. Once a patient relapses, the effectiveness of allogeneic bone marrow transplantation is more pronounced. Transplantation for a second or subsequent complete remission or transplantation at the time of relapse has a significant survival advantage in favor of transplantation (Table 2), since long-term disease-free survival even in children given chemotherapy is less than 20%. In children with remissions of less than 18 months, there were no survivors.[60] A randomized study for patients not in their first complete remission, with randomization based on the availability of a histocompatible donor, has been carried out in Seattle. The results strongly favor the use of bone marrow transplants.[61,62] New combinations of chemotherapy such as etoposide and fractionated total body irradiation result in an actuarial disease-free survival rate at three years of 43% to 56%, even in patients not in first remission.[56,63]

Acute Nonlymphoblastic Leukemia

Patients with acute nonlymphoblastic leukemia or acute myelogenous leukemia clearly benefit from transplantation. Randomized studies comparing allogeneic bone marrow transplantation with intensive chemotherapy show improved results with transplantation.[64-66] When allogeneic transplantation is carried out in patients younger than 40 in first complete remission, they can expect an actuarial disease-free survival of 45% to 65% at five years and are probably cured.[67-69] Again, where transplantation is carried out during the second or subsequent complete remissions or in relapse, bone marrow transplantation is clearly superior to chemotherapy (Table 2).

Chronic Myelogenous Leukemia

Allogeneic bone marrow transplantation has been carried out for chronic myelogenous leukemia (CML) for more than a decade. Although early results of transplantation for CML in the blast phase were discouraging,[70] when transplantation is done during earlier stages, namely the chronic phase, the results have been promising. Long-term remission can be achieved in 55% to 75% of these patients.[48,70-72] There are several features unique to CML. The definition and clinical significance of relapse are unclear. That is, a patient with the Philadelphia (Ph) chromosome before a transplant may, after transplant, be Ph-negative and remain so; remain Ph-positive in clinical remission, or subsequently relapse; or remain Ph-negative initially, and then become Ph-positive with or without a clinical relapse.[73-77] Even when a relapse is established histologically, the disease can sometimes behave indolently. Prospective studies with long-term follow-up of patients are needed to establish the importance of these findings.

Another feature unique to chronic myelogenous leukemia is the timing of the transplant. Because CML is a chronic and heterogeneous disease, patients may stay in the chronic phase for years. Research efforts have been directed to establish the optimal time for a bone marrow transplant. Data from the Seattle group and the International Bone Marrow Registry suggest that the sooner a patient has a transplant following diagnosis, the better the outcome.[71,72] There are also new methods with the potential to select those patients whose clinical characteristics at presentation to medical care put them at a higher risk. There are data to suggest that the position of the breakpoint cluster region (bcr) may have prognostic significance.[78-80] Finally, with the recent introduction of interferon-α and the observation that it can in rare instances even induce Ph chromosome negativity, the timing of allogeneic bone marrow transplantation again has been called into question.[81] Several investigators have proposed a trial of interferon-α as a reasonable alternative path.

Severe Aplastic Anemia

Allogeneic bone marrow transplantation for severe aplastic anemia has become the standard of care for young patients with HLA-matched donors. Results from the Seattle group show a disease-free survival rate of 80% for those patients with severe aplastic anemia who were not transfused

TABLE 2.—*Long-Term, Disease-Free Survival in Continued Complete Remission Following Bone Marrow Transplantation in Relation to Pretransplant Remission Status*

Allogeneic Bone Marrow Transplants			*Autologous Bone Marrow Transplants*	
ANLL, %	*ALL, %*	*CML, %*	*Hodgkin's Disease, %*	*Non-Hodgkin's Lymphoma, %*
1st CR, 45-65	1st CR, 50-65	1st and 2nd chronic phase, 55-75	"Good risk" relapse, 60-70	"Sensitive relapse," 65-70
2nd CR, 1st relapse, 20-45	2nd CR, 1st relapse, 30-45	Accelerated phase, 30-40	"Poor risk" relapse, 15-20	"Resistant relapse," 10-15
3rd and subsequent CR, advanced relapse, 10-25	3rd and subsequent CR, advanced relapse, 15-25	Blastic phase, 5-15		

ALL=acute lymphoblastic leukemia, ANLL=acute nonlymphoblastic leukemia, CML=chronic myelogenous leukemia, CR=complete response

before having an allogeneic bone marrow transplant, compared with 45% to 50% for those who were transfused. The maximum follow-up time has now reached 17 years.[82] Certain criteria have been established to identify a population of patients with a poor prognosis:

- A marrow cellularity of less than 25% of normal, or less than 50% of normal with less than 30% hematopoietic cells;
- At least two of these blood values: granulocyte count of less than 0.50×10^9 per liter (500 per μl), a platelet count of less than 20×10^9 per liter (20,000 per μl), or anemia with a corrected reticulocyte count of less than 0.01 (1%).[83]

In contrast to allogeneic bone marrow transplants for malignant diseases, in transplantation for severe aplastic anemia, graft rejection is more frequent.[84,85] This is related partly to patients' sensitization by previous transfusions and to the preparative regimen, which usually consists of using only cyclophosphamide. Cyclophosphamide as a single agent is probably not sufficiently myelosuppressive for all patients with severe aplastic anemia. There have been some reports of autologous recovery of bone marrow following rejection.

Other Diseases

A small number of patients have received transplants for various malignant and nonmalignant disorders. With the recognition that immune cells arose from the bone marrow, transplantation became an attractive method to correct immunodeficiencies such as severe combined immunodeficiency,[36,37,86] Wiskott-Aldrich syndrome,[87] congenital leukocyte dysfunction syndromes,[88,89] and osteopetrosis.[90-93] Unique to the group of patients with immunodeficiency is the realization that HLA-mismatched grafts can be done successfully, especially in those patients who lack a T-cell response toward allogeneic targets.

With the knowledge that the reconstitution of bone marrow resulted in a correction of immunodeficiencies and that bone marrow cells led to the long-lived macrophages, interest grew in using allogeneic bone marrow transplantation for correcting lipidoses, such as Gaucher's disease[94] or Wolman disease,[95] and also the possibility of replacing the missing enzymes in severe combined immunodeficiency disorders such as adenosine deaminase-deficiency,[96] Fabry's disease,[97] Hurler's syndrome, and other mucopolysaccharidoses.[98-102]

Transplantation is also carried out successfully for other hematologic disorders. Lucarelli and colleagues in Italy have reported excellent results in young patients with thalassemia major.[103] Transplantation has also been done for other hematologic disorders such as hemoglobinopathies,[104] paroxysmal nocturnal hemoglobinuria,[105-108] congenital pure red cell aplasia,[109] Diamond-Blackfan anemia,[110] and Fanconi's anemia.[111,112] The results of transplantation for Fanconi's anemia are not as encouraging. These patients seem to have a systemic constitutional defect resulting in poor tolerance of high-dose chemotherapy. Finally, small numbers of transplants have been carried out with encouraging results for myelodysplastic syndromes, secondary leukemia, and acute "malignant myelosclerosis."[113-115]

Future Directions

As marrow transplantation in humans enters its third decade, a review of past achievements is rewarding. Progress has been slow and cumbersome, but allogeneic bone marrow transplant is now a well-accepted form of therapy for a number of diseases. Although progress for the third decade should be more rapid as large numbers of patients undergo transplantation, the procedure should still be part of well-designed and carefully conducted cooperative clinical trials, especially as it is done in a larger number of small centers.

There are several exciting prospects for research and development:

Graft-Versus-Host Disease

T-cell depletion may be a reasonable option for preventing graft-versus-host disease if there is no significant graft failure or late recurrences of malignant disease with longer follow-up. To date, most of the T-cell depletion studies have reported a higher recurrence rate or graft failure. Most likely the data from animal models, where a titrated number of specific T cells are returned, may allow investigators to prevent graft-versus-host disease without the loss of a graft-versus-leukemia effect or an increase in graft rejection.[53]

Monoclonal Antibodies

One of the methods developed for T-cell depletion and therapy for graft-versus-host disease is monoclonal antibodies. These can be coupled to toxins or radioisotopes and directed against specific targets. Monoclonal antibodies may also be used as a cytoreductive method before transplantation. Manipulation of the immune system, by using a monoclonal anti-idiotype of a tumor, may enhance immunity against the tumor before or after transplantation.

Interstitial Pneumonia

Cytomegalovirus, which previously led to lethal pneumonias, may now be adequately treated with a combination of ganciclovir and immunoglobulin G. More exciting is the prospect that the use of these agents prophylactically may significantly reduce the mortality from interstitial pneumonia.

Unrelated Donors

As the number of registered volunteer donors grows, the chances of finding an unrelated HLA-matched donor will increase substantially. The increased chance of locating a matched donor, in conjunction with newer methods to prevent graft-versus-host disease, may allow allogeneic transplantation to be accomplished safely in a larger number of patients.

New Regimens

As discussed previously, new combinations of active agents such as fractionated total body irradiation and etoposide have lowered the rate of relapse from leukemias. As the understanding of human immunology improves and the cellular communication mechanisms are understood, new agents may become useful in transplantation. These include direct toxins such as interferon or interleukin-2 and adoptive cell transfers such as lymphocyte-activated killer cells or tumor-infiltrating lymphocytes. With the advent of molecular cloning, various growth factors have been introduced into clinical trials. Whether these will prove to be useful in marrow transplantation will have to await the results of ongoing randomized clinical trials.

Gene Transfer

Gene transfer is widely done in the laboratory. There has been a great interest in using gene transfer in animals and ultimately as therapy for human diseases. The use of appropriately altered retroviral vectors may provide the ultimate correction of certain genetic diseases—thalassemia major, for example—in conjunction with transplanted bone marrow. Clearly, concerns for the infectivity of the virus and oncogenicity will have to be allayed before this approach can be used in humans.

Stem Cell Isolation

With the murine pluripotent stem cell isolated by Weissman's group,[116] there is a great deal of excitement, with notable efforts being made to isolate the human stem cell. Partially purified "stem cells" have been used for transplant in baboons, with limited success.[117] When this is feasible in humans, various difficulties with allogeneic bone marrow transplants should be lessened.

Finally, as molecular biology and genetic engineering, immunology, pharmacology, and clinical medicine develop, bone marrow transplantation is a field where all can contribute and merge meaningful data for the best outcome for patients.

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Medical Staff Conference

Update on Pseudomembranous Colitis

Discussant
JOSEPH SILVA, Jr, MD

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Every advance in medicine has its costs, and one of those associated with potent, often life-saving antibiotics is pseudomembranous colitis. I am pleased that my colleague at the University of California, Davis, Joe Silva, will review at this conference the important features of this disease, including its diagnosis, treatment, and prevention.*

JOSEPH SILVA, Jr, MD†: In 1893 Finney of Baltimore described pseudomembranous colitis in a patient who had recently undergone a gastrointestinal surgical procedure. Before the advent of antibiotics, as many as four to six cases would occur each year in large hospitals, generally following surgical treatment of the upper gastrointestinal tract. The frequent use of broad-spectrum antibiotics in the late 1960s to mid-1970s caused pseudomembranous colitis to become a frequent clinical disorder. In the days before the cause and appropriate treatment of pseudomembranous colitis were known, the mortality in symptomatic patients was as high as 20% to 25%. A little more than ten years ago, several groups determined that the disease is caused by colonic infection with toxigenic *Clostridium difficile,* a fastidious gastrointestinal anaerobe.

Clostridium difficile as a Pathogen

For many years, *C difficile* was infrequently identified as a cause of infection and was most often isolated in a cluster of other bacteria cultured from intra-abdominal abscesses, osteomyelitis, or gangrenous tissue. Small's discovery in 1969 that lincomycin hydrochloride induced fatal colitis in hamsters[1] led to a useful model that ultimately identified *C difficile* as the cause of pseudomembranous colitis in humans.[2-4] This anaerobic organism is a gram-positive, 15- to 20-μm bacillus that produces subterminal spores. The ability of these spores to survive for many years in an aerobic environment on inanimate surfaces may contribute to the greater incidence of colonization and of pseudomembranous colitis in patients in hospital.[5] Some 3% to 6% of healthy humans carry *C difficile,* and this prevalence may double or triple in patients in hospital. Colonization in these patients is related to the frequent prolonged use of high doses of antibiotics, which may radically alter the anaerobic microbial flora within the gastrointestinal tract. The incidence of colonization by *C difficile* is further increased in patients in hospital by manipulation of the intestinal tract, such as during the use of nasogastric tubes or enemas. Although *C difficile* is one of the first anaerobes to colonize the intestinal tracts of newborns, it almost never causes any clinical disease in this population. One possible reason for this paradox may be gleaned from preliminary data suggesting that neonatal tissues lack appropriate intestinal receptor sites for the toxins of *C difficile.*

Clostridium difficile appears to produce at least four toxins, two of which have been well characterized.[6] Toxin A (also called enterotoxin or D-1) is thought to account for much of the morbidity in the hamster model and in humans. This enterotoxin leads to perturbations in brush border function and in water transport across the intestinal tract; it is lethal to rodents. Toxin B (also named cytotoxin, or D-2) is defined by its primary effects on in vitro cell cultures of mammalian fibroblasts. The cytotoxin alters adenosine diphosphate ribosylation, thereby altering polymerization of intracellular actin filaments. As a result, actinomorphic changes occur 4 to 24 hours after inoculation of toxin B onto a monolayer of fibroblastic cells such as those used in isolating viruses. It appears that most clinical specimens isolated from patients are toxigenic, whereas as many as 20% to 25% of environmental isolates are nontoxigenic. Toxin B (cytotoxin) and toxin A (enterotoxin) are conjointly produced by most organisms that have been studied.

Clostridium difficile also produces two other toxins that interrupt gastrointestinal peristalsis. Toxins A and B are destroyed in vitro if subjected to repetitive cooling and warming. This fragility accounts for some of the varying results obtained by commercial laboratories testing for cytotoxin—false-negative results. Hamsters can be passively immunized and partially protected with γ-globulin against antibiotic-induced *C difficile* colitis.[7] Current efforts to develop toxoids are still fairly nascent, although it has been shown in the hamster model that a toxoid to the enterotoxin can induce immunity, whereas a toxoid to the cytotoxin does not.[8]

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Clinical Spectrum of Pseudomembranous Colitis

The principal symptom of pseudomembranous colitis is diarrhea. A useful clue to the diagnosis of colitis is the production of five or more loose stools a day.[9] Stools of patients with *C difficile* colitis are generally watery and small in volume and frequently contain mucus. It behooves clinicians to inquire of all patients who have watery diarrhea whether they have been taking antibiotics during the previous six weeks. Diarrhea develops in 15% to 25% of patients with pseudomembranous colitis after they discontinue their antibiotic(s). Physicians should also educate patients to report any diarrhea that exceeds five loose stools a day while receiving antibiotics. The pattern of diarrhea may be intermittent, with normal defecation for one to two days interspersed with days of five to ten episodes of diarrhea. Mucus is commonly noted in the stool, but blood is not. Many of our patients with colitis have negative fecal tests for occult blood. An increased number of fecal leukocytes are reported by some investigators, but in my experience this occurs in only about a third of specimens.

The clinical spectrum of pseudomembranous colitis is changing as assays for discovering the fecal toxins of *C difficile* become more available and employed. *Clostridium difficile* also can induce a syndrome of colitis that is well localized to the cecal area, and patients with this syndrome may not have diarrhea. Some also have hectic fever of >40°C (104°F) or fever of unknown origin, with minimal or no diarrhea. Other patients may have toxic megacolon or acute peritonitis. Physicians should be aware that the symptoms of pseudomembranous colitis may resemble those of an acute abdomen, and an inquiry should be made about recent antibiotic use.[10] Taking an astute history may spare a patient a laparotomy and will lead to appropriate treatment with an oral antibiotic regimen designed to eradicate *C difficile* from the colon.

Another form of clostridial enterocolitis occurs in patients with neutropenia from cancer chemotherapy.[11] The disorder of hemorrhagic or necrotizing cecitis (or typhlitis) is seen primarily in young patients who have leukemia. These patients usually have hectic fever, minimal stooling, and signs of an acute abdomen. Roentgenographs of the abdomen frequently show an absence of air in the right lower quadrant. The morbidity of this form of cecitis is high because of transmural inflammation and the high concurrence of bacteremia. Hematologists and oncologists must be aware of this disease, as it can be induced not only by antibiotic use but also by cytotoxic chemotherapeutic programs alone.[12] The progression from the onset of symptoms to death is rapid, occurring over a span of two to three days.

Pathogenesis and Incidence of Pseudomembranous Colitis

It is important to differentiate diarrhea with colitis from simple antibiotic-associated diarrhea. The latter state is more of a nuisance phenomenon in which the stools are malformed and watery. It is unassociated with constitutional symptoms, and there is so far no evidence that *C difficile* or its toxins play an etiologic role. Simple antibiotic-induced diarrhea is common and occurs with antibiotic therapy in 3% to 10% of adults and children, with generally a higher rate in children.

The incidence of *C difficile* colitis is not well ascertained. Several studies of outpatient populations indicate a frequency of 1 to 3 cases per 100,000 patients being treated with an oral antibiotic (Table 1).[13] The incidence in patients in hospital may be as high as 1 per 100 to 1,000 inpatients and varies by hospital, according to the patient mix. The cause of colitis is related to the reduction of certain elements of the normal fecal flora, allowing *C difficile* to find an ecologic niche; a reduced number of anaerobes is probably more important than similar effects in the aerobic flora. It is clear that several nonclostridial anaerobes play a role in restraining growth or toxigenesis, or both, of *C difficile* both in vitro and in vivo.

TABLE 1.—*Antibiotic-Related Gastrointestinal Side Effects*

Diarrhea—%	
Adults	3-10
Children	3-15
Colitis—Incidence	
Outpatients	1-3/100,000
Inpatients	1/100-1,000
Third-generation cephalosporins	1/1,000-2,000

The major cause of pseudomembranous colitis is the use of antibiotics. In my experience, ampicillin sodium, cephalosporins as a generic group, and clindamycin phosphate are the most frequent inducers; all antibiotic classes have been associated with pseudomembranous colitis, however, including even those that are effective in treating it—vancomycin hydrochloride and metronidazole hydrochloride, for example.[14] Colitis can be induced with only one or two doses of an antibiotic and can occur with intravenous, oral, and topically administered antibiotics. The tragedy is that some cases are precipitated by the use of antibiotics to treat viral syndromes or pseudoinfections, where antibacterial antibiotics play no discernible therapeutic role.

We are also now recognizing that pseudomembranous colitis can occur spontaneously without the use of antibiotics (Table 2). Pseudomembranous colitis has been described in patients with insulin-dependent diabetes mellitus, hepatic and renal failure, malnutrition, cystic fibrosis, and following upper gastrointestinal tract surgical procedures. In my experience, patients who are maintained at complete bed rest, particularly because of neurologic diseases or gastrointestinal dysautonomia, or both, are subject to spontaneous occurrences. The use of cytotoxic drug therapy such as methotrexate sodium or 5-fluorouracil can also induce pseudomembranous colitis, even when antibiotics are not being given.[12] These latter drugs have very modest to nil antibacterial activity but may create the syndrome by altering host defenses or subtly altering bacterial flora in the colon. The point is that while 99% of cases of pseudomembranous colitis are related to antibiotic use, other cofactors of induction increasingly are being recognized.

Diagnosis of Pseudomembranous Colitis

A diagnosis of pseudomembranous colitis is very dependent on the taking of an adequate history, one focusing on the taking of antibiotics and other drugs that could induce this disease. A physician also should consider other causes of inflammatory colitis, such as *Entamoeba histolytica, Strongyloides* and *Campylobacter* spp, *Staphylococcus aureus, Candida* sp, and *Mycobacterium tuberculosis.* The major assay for diagnosing pseudomembranous colitis uses cultures of tissue to detect the cytotoxin in fecal specimens rendered free of bacteria by filtration. Specific antiserum

TABLE 2.—*Factors Rendering Immunocompromised Patients at Risk for Toxic Enterocolitis*

Cystic fibrosis	Renal failure
Bed "bound"	Malnutrition
Neurologic disease	Surgical procedure
Intensive care units	Leukemia
Hepatic failure	Cancer chemotherapy

also is available to neutralize the actinomorphic changes caused by cytotoxin in these tests, which greatly increases the specificity of the results. In the experience of most investigators, 90% to 95% of patients whose feces are positive for cytotoxin have colitis as determined by visualization or colonic biopsy.[15] The latter test is the "gold standard." While patients have been described as having colitis specifically isolated to the cecum or ascending colon, this is uncommon in my experience. Almost all patients can be diagnosed by flexible sigmoidoscopy, for the descending and sigmoid colons are where the action is.[16] It is most important to do a biopsy of the colonic mucosa. Experienced gastroenterologists have proclaimed colons as being normal when viewed through a proctoscope, only to be surprised when the histopathologic evaluation reveals early colitis.

The range of lesions is extensive, from focal or granular colitis (mucositis), to diffuse erythema, to the development of plaques or extensive pseudomembranes. The pseudomembrane is composed of fibrin, bacteria, degenerating leukocytes, and epithelial cells. In addition, it is possible to visualize colitis in some patients by using tomographic scans of the abdomen or radionuclide tests such as indium-labeled leukocytes or gallium citrate Ga 67 scans, or both. These procedures are helpful in puzzling cases where the cytotoxin assays of fecal samples do not give clear-cut results.

A latex agglutination method now is available for detecting *C difficile* toxins in stool samples.[17] It appears, however, that this assay detects not only the toxins of *C difficile* but cellular components of other anaerobes frequently contained in normal stools. The frequency of positive results in known cases of pseudomembranous colitis may be only 60% to 80%, and the rate of falsely negative results is also high, making this an uncertain assay at the current time. A selective culture medium has also been developed that may detect as few as 1,000 colonies of *C difficile* per gram of wet weight of feces.[18] Fecal cultures for *C difficile* are generally used for research purposes, although one study has suggested that this test may play a collaborative role in determining clinical disease.[19] This culture may be useful, for example, in a patient who is not acutely ill—such as one who does not warrant empiric antibiotic therapy—or who has an unusual clinical presentation of colitis and is undergoing an extensive workup. I have seen patients with colitis in whom the cytotoxin assays of their stools were negative because of low titers of toxin in one or two specimens, while at the same time the fecal culture was positive. This latter test then served as the stimulus to do sigmoidoscopy or obtain additional fecal specimens for cytotoxin testing, which then were positive for *C difficile.* We often are uncertain of the reason(s) for the unclear endpoints in the cytotoxic assay sometimes obtained with specimens of feces from colitis patients. Hypotheses have included partial binding of the toxin by coproantibodies or alteration of the toxin by other microorganisms or substances, or both. This is an interesting area for further investigational pursuit.

Treating Pseudomembranous Colitis

After diagnosis, treatment of pseudomembranous colitis must begin promptly. In most clinically nontoxic patients with early pseudomembranous colitis, discontinuing the offending antibiotic or drug regimen is often sufficient. If the patient continues to have diarrhea over the next day or two or appears ill when initially diagnosed as having colitis, then antibiotic treatment should be promptly and empirically instituted to eradicate *C difficile* from the colonic flora. Because of the morbidity of colitis, any toxic patient with a potential for having pseudomembranous colitis should receive antibiotics effective against *C difficile* after a stool specimen and the other appropriate diagnostic studies are obtained. Fecal specimens can be saved for cytotoxin analysis at night by freezing—the colder the better.

Clostridium difficile has a variable sensitivity to antibiotics. In vitro, it is readily sensitive to penicillin and ampicillin, vancomycin, metronidazole, and bacitracin.[20] In the United States and other countries, there is a "neck-and-neck" race between orally administered vancomycin and metronidazole as to which is the drug of choice. Occasional isolates of *C difficile* are resistant to metronidazole, and I also have noted in some very ill patients with colitis that metronidazole appeared to work less rapidly than orally administered vancomycin.

While 500 mg of vancomycin given orally four times a day was used in some of the original studies, it is now clear that a dose of 125 mg four times a day is adequate to produce abundant and effective fecal concentrations in the colon to eradicate *C difficile.*[21] The dose of metronidazole administered orally varies between 250 mg and 500 mg three to four times a day.[22] Most patients are treated with either antibiotic for seven to ten days, recognizing that small amounts of the antibiotic are continually eliminated over several days following the cessation of therapy. In a comparative study of metronidazole versus vancomycin, they appeared equally efficacious, although the cost of metronidazole was less.[23] A course of vancomycin (given 125 mg four times a day) costs approximately $115 to $150 in California; metronidazole can be given at a quarter or less of this cost. Bacitracin administered orally also appears to be effective, but it is less readily available and is more expensive than metronidazole.[24] A recent report also describes teichoplanin as an effective oral antibiotic.[25]

Antiperistaltic drugs should be avoided because they may prolong the fecal carriage of the organism and may make a patient sicker. Corticosteroids—given either orally, parenterally, or by enema—have no role in treatment. Unfortunately, resection of the colon is sometimes required because the disease is diagnosed late after the onset of symptoms. Cholestyramine has been used in the past as a binder of the toxins (it does so in vitro) but, in my opinion, has only modest therapeutic effects.

A real dilemma is how to treat a patient with pseudomembranous colitis who cannot take any oral medications because of nasogastric suctioning, bowel diversions, or ileus. There have been scattered reports—and I have seen several such cases—of pseudomembranous colitis occurring while a patient was receiving intravenous metronidazole or vancomycin. The fecal concentrations achieved by intravenous in-

fusions of these two antibiotics are generally not adequate to eradicate *C difficile* from the colon. Some investigators state that to achieve some antibiosis in the colon of adults who cannot take oral drugs, vancomycin should be given at a daily dose of at least 2 grams intravenously. For these patients, I have recommended that vancomycin should also be given by enema, using a solution of 500 mg in 1 liter of a saline solution given by enema every eight hours with gentle pressure. If a patient cannot retain the enema, a Bardex catheter, as is employed in barium enemas, can be used. Others are experimenting with placing a long catheter into the small intestine and then infusing vancomycin in similar concentrations (500 mg per liter) at 1 to 3 ml per minute (T. Nostrant, MD, University of Michigan, oral communication, January 1989). If a patient truly is not responding to vancomycin by either of these routes, then a colostomy or cecostomy can be done and the antibiotic instilled directly into the colon. Other investigators are experimenting with the transabdominal injection of vancomycin into the colon under colonoscopic control. This therapy is controversial at this time, and it is uncertain if other antibiotics that are effective against *C difficile* in vitro, such as ciprofloxacin hydrochloride, will achieve favorable fecal concentrations when given orally or intravenously.

Isolation Considerations

Another important goal in treating pseudomembranous colitis is to restrict the organism to a specific patient. Environmental cultures done in several centers have indicated that defecation by a patient with symptomatic pseudomembranous colitis[26,27] causes a scattering of *C difficile* into the vicinity. The organism can be recovered from surfaces in the rooms of symptomatic patients, such as bedclothes, sheets, pillows, bed stands, sinks, and toilet seats, in the vicinity of where defecation occurred. This environmental shedding is notably less in patients who are carriers of this organism and have no diarrhea.

There have been outbreaks of *C difficile* occurring in clusters in specific locations within hospitals throughout the world.[28,29] Other reports suggest that the organism can settle in and cause repetitive nosocomial infections.[29,30] This anaerobe's ability to produce spores enables it to survive in a hospital environment, and measures to reduce its nosocomial effect are important.

The organism can be carried on the hands of medical personnel and on medical equipment. I have even isolated it from communal wheelchairs at our hospital. The importance of this form of possible transmission needs further study. Larson and co-workers have shown in hamsters that one colony-forming unit of *C difficile* placed into the mouth after one antibiotic dose will induce fatal colitis.[30] The use of enemas or nasogastric tubes has been implicated as a cofactor in inducing this disease in patients in hospital[28]; other causes are colonoscopy, antacids, and upper gastrointestinal operations. The spores are generally resistant to the quaternary ammoniacals or phenolics that hospitals use as general disinfectants. Only the use of alkaline glutaraldehyde or phosphate-buffered hypochlorite solutions are effective against *C difficile* spores in vitro. These agents are either carcinogenic (alkaline glutaraldehyde), so they must be contained in protected areas, or corrosive to surfaces (phosphate-buffered hypochlorite), which make them unsuitable for general decontamination of the environment.

TABLE 3.—*Treatment of Relapses in* Clostridium difficile *Infection*

Repeat vancomycin, 500 mg 4 times a day by mouth × 14 days
Slow taper of vancomycin over 2 to 3 months
Tyndallization with vancomycin
Antibiotic combinations
Vancomycin + metronidazole
Vancomycin + rifampin

In the setting of a cluster, or even with one patient with pseudomembranous colitis, isolation techniques that restrict stool contamination must be prescribed. All personnel having direct contact with these patients, their feces, and their immediate environment should wear a gown and gloves, and thorough hand washing must follow this contact. In settings of clusters in closed units, other measures used have included cohorting of patients and other isolation "barrier" techniques. Sometimes the prophylactic use of vancomycin or metronidazole has been prescribed for all patients housed in the area to blunt the transmission of this organism and the subsequent onset of colitis.

Relapses After Termination of Therapy

Some 10% to 14% of patients with *C difficile* infection relapse following termination of either orally administered metronidazole or vancomycin. A similar relapse rate is also seen with bacitracin. The reasons for these relapses are not known, but they appear to result from reinfection with the same organism either from remote areas of the colon that were not adequately sterilized with the antibiotic course or by reinfection from the environment. I have seen one patient who suffered relapses for two years before this microorganism was eradicated. Several approaches to treating relapses are outlined in Table 3. One of the more frequently used methods is to treat patients with the alternative antibiotic—if vancomycin was the antibiotic given initially, then metronidazole would be administered, or vice versa—with treatment generally prolonged to two weeks. If the patient has an additional relapse, some success may be obtained by using oral vancomycin at a dose of 500 mg four times a day, plus oral rifampin, 600 mg twice a day, for they are synergistic in susceptibility tests for *C difficile.*[32] Others have combined vancomycin with metronidazole, but I have no experience with the regimen. If a patient relapses following a second course of treatment, I recommend a course of vancomycin for two to three months with a slow taper in both dose and frequency of administration.[33] Tyndallization is a British approach in which vancomycin is given intermittently for two to three days, separated by a similar time period. Intermittent proctoscopy also should be done to exclude other colonic disorders such as Crohn's disease.

Another exciting approach to treating relapses is the use of biotherapy. It has been shown in hamsters that feces obtained from normal hamsters and given by enema—or nontoxigenic *C difficile* isolates given orally—can prevent induction of *C difficile* colitis following challenges of an antibiotic that ordinarily causes their death.[34] Recently investigators reported using an enema of a solution containing ten bacteria to inhibit *C difficile* relapses in six patients.[35] It appears that in vitro some strains of *Enterococcus faecalis, Escherichia coli, Saccharomyces boulardii, Clostridium beijerinckii,* and several bacteroid species *(Bacteroides ovatus,*

Bacteroides vulgatus, and *Bacteroides thetaiotaomicron)* can influence the growth of *C difficile* or its toxigenesis or both. The compounding of these organisms in a capsule for more palatable oral administration would be an important advance. Monospecific biotherapy by mouth has also been successful in a small number of patients: lactobacilli have been used to treat relapses, and *S boulardii* given concomitantly with antibiotic therapy reduces the frequency of *C difficile*-associated diarrhea.[36,37]

Summary

Thousands of cases of pseudomembranous colitis occur annually in the United States. Physicians giving antibiotics must advise patients to report any substantial diarrhea and be aware of the variety of clinical presentations of *C difficile* infection and the nuances of its treatment. The morbidity and mortality of toxic enterocolitis clearly can be reduced, but, unfortunately, patients still die of this disease. These deaths are preventable if physicians are aware of the problem. The eventual establishment of an effective toxoid—immunization is already used for another *Clostridium* species, *tetani*—and effective bacteriotherapy are exciting treatment modalities that may eventually eliminate this disease.

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Epitomes

Important Advances in Clinical Medicine

Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Cutaneous Manifestations of Human Immunodeficiency Virus Infection

CUTANEOUS DISEASE is extremely common in persons infected with the human immunodeficiency virus (HIV), with an incidence approaching 100%. Early in the course of the infection, often the only or most prominent manifestations are changes on the skin. Skin problems continue throughout a patient's lifetime and often notably reduce the quality of life because of the severity of the symptoms or the cosmetic consequences. Skin disorders seen in an HIV-infected person can be grouped into three large categories: infectious diseases such as persistent herpes simplex, mucocutaneous candidiasis, oral hairy leukoplakia (Epstein-Barr infection of the lateral aspects of the tongue), widespread or extensive facial molluscum contagiosum, dermatophyte infection, and bacterial folliculitis; noninfectious inflammatory diseases such as frequent drug reactions (especially to the combination of sulfamethoxazole and trimethoprim), seborrheic dermatitis, psoriasis, and other poorly understood pruritic dermatoses; and neoplasms such as Kaposi's sarcoma and lymphoma. In addition, HIV infection may prematurely age a person, leading to excessively dry skin, premature graying, and diffuse alopecia.

Infectious diseases, as a consequence of suppression of the immune system, still represent a major problem. Herpes simplex and herpes zoster are common, and now acyclovir-resistant strains have caused disease in patients with the acquired immunodeficiency syndrome (AIDS). A bacterium identical to or closely related to the agent causing cat-scratch disease has been shown to cause a chronic systemic infection in patients with AIDS or the AIDS-related complex. Skin lesions are usually the initial manifestation and appear as angiomatous papules, subcutaneous nodules, or cellulitic plaques. In addition, bone lesions and widespread visceral involvement may occur. Some of the initially identified patients died of airway obstruction. Erythromycin therapy is curative.

While the immune system is suppressed and unable to handle certain infectious diseases effectively, cutaneous hyperreactivity may also be seen. Pruritic dermatoses such as atopic dermatitis, photosensitivity, drug reactions, and severe insect bite reactions also may occur. These pruritic eruptions are still largely uncharacterized but substantially reduce a person's quality of life, especially those with otherwise minimally symptomatic disease. In Africa and Haiti pruritic eruptions are the initial manifestation of HIV infection in about 50% of patients.

Kaposi's sarcoma remains the most common malignant neoplasm in AIDS patients but appears to be largely restricted to homosexual and bisexual men. While the total number of cases continues to increase, the incidence is falling. Therapy includes both local treatment such as radiation therapy or intralesional administration of vinblastine sulfate or systemic therapy such as interferon-α or single or combination chemotherapy. The response rates are lower than those seen in patients with classic Kaposi's sarcoma, however.

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Diet and Atopic Dermatitis

DIET RELATES TO atopic dermatitis in two main areas: food allergy and nutrition. Cases of food allergy exacerbating atopic dermatitis have been reported sporadically since the 1930s, and clearly some patients have itching and erythematous flaring after eating foods to which they show positive results on skin tests. Points of controversy include the incidence of true food-induced flaring of atopic dermatitis and the latent period after ingesting the allergen. While many investigators insist on the existence of delayed responses, even as long as four days after food ingestion, such claims are hard to prove given the myriad of other trigger factors that might be active during a prolonged period. The only reactions subjected to rigorous proof have been those of relatively rapid onset, with morbilliform lesions and itching present 30

to 120 minutes after a double-blind food challenge in a large series of children. These reactions are often accompanied by gastrointestinal and respiratory symptoms and elevations of plasma histamine levels. The most common offending food allergens are egg, milk, peanut, seafood, wheat, and soy. Avoiding offending foods is generally associated with an abatement of the dermatitis. Follow-up studies have shown a loss of sensitivity with age in some children.

Incidence and prevalence figures cannot be gleaned from these studies as the subjects represent a highly selected, university referral population. A reasonable estimate suggests that 10% to 20% of children and less than 10% of adults have worsening of their eczema because of food allergy. Scratch test results and serum radioallergosorbent test levels show 80% false-positivity, but negative tests are 90% reliable in ruling out food-induced dermatitis. Restricting suspect foods to allow clearing of the dermatitis—usually for three to seven days—followed by challenge, in a blind manner, if necessary, is the only sure means of diagnosis. Wide-ranging restrictions based on positive skin tests are unreasonable and can lead to malnutrition. Restricting highly allergenic foods such as cow's milk, eggs, or peanuts from infant diets, while of unproved efficacy, may be worthwhile for the offspring of highly atopic parents, especially those with atopic dermatitis.

The main focus of the nutritional aspects of diet in atopic dermatitis has been, in recent years, the feeding of evening primrose oil. This may have originated from the erroneous association between eczematous skin and cutaneous changes induced by essential fatty acid deficiency. A later conceptual rationale implied that replacing deficient γ-linolenic acid (GLA), present in varying concentrations in evening primrose oil, might correct changes induced by excessive arachidonic acid-derived, proinflammatory eicosanoids. While the results of one clinical trial suggested positive effects, a subsequent study failed to detect any therapeutic benefit. Newer research indicates that high doses of GLA may have antileukotriene effects and a therapeutic benefit in some patients. A final resolution of this contentious issue requires controlled therapeutic trials with standardized material of known GLA content and careful monitoring of skin delivery. At present, dietary treatment with currently available evening primrose oil cannot be recommended for atopic dermatitis.

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Copper Vapor and Dye Laser Therapy for Cutaneous Vascular Disorders

SINCE THEY WERE FIRST introduced in the early 1960s, visible light lasers have played an important role in treating vascular conditions. Initially the blue-green light from the argon laser was used because its emission overlapped the absorption spectrum of oxyhemoglobin. It became readily apparent, however, that this laser-tissue interaction was imprecise and that there was also interference resulting from absorption by the melanin found in the overlying epidermis. The combined effect was the occasional production of scarring or permanent textural changes that provided an unsatisfactory cosmetic result.

As a consequence of these unacceptable side effects, improved light sources for treating vascular conditions have long been awaited, and recently three new laser systems have been developed, all of which are capable of producing yellow light. Improved laser-tissue interaction is possible with the use of yellow light at a wavelength of 577 nm because it is precisely absorbed by oxyhemoglobin at its β-absorption peak. In addition, absorption interference by epidermal melanin is substantially reduced at this longer wavelength, so there is less damage to the skin surface.

The argon-pumped tunable dye laser, the first of these new systems to be introduced, uses an argon laser to energize an organic dye solution to produce yellow light having a continuous output. Although this laser light can be mechanically or electronically pulsed, the duration of these pulses is relatively long—on the order of 0.05 seconds. Light from this laser typically is delivered in slightly overlapping 1- to 2-mm spots to the surface of large vascular lesions like port-wine stains or at spaced points along the length of telangiectatic blood vessels.

A new technique has been developed that uses a small beam (100 μm) from an argon-pumped tunable dye laser. With low power—0.08 W to 0.18 W—and continuous discharge, individual blood vessels in port-wine stains or telangiectasia are traced out and removed with the aid of magnified vision. This technique spares injury to the adjacent normal skin, minimizes damage to the overlying epidermis, limits postoperative wound care, and permits a rapid clearing of the vessels. Furthermore, in many cases substantial improvement can be seen after only a single treatment. This procedure permits safe and effective treatment of port-wine stains found even in areas that traditionally have been associated with a high risk of scarring, such as the upper lip and lateral neck. Children with port-wine stains also may be treated without substantial risk of scarring.

More recently, the use of short pulses of laser light to damage blood vessels selectively has been made possible with the introduction of a second type of dye laser, the flash-lamp-pumped pulsed dye laser. This laser system uses a flash lamp to energize an organic dye solution, which yields a 3- to 5-mm beam of yellow light at either of two wavelengths: 577 nm or 585 nm. The flash-lamp-pumped pulsed dye laser produces very short pulses of light—from 360 to 450 microseconds in duration—that closely approximate the thermal relaxation time for small blood vessels. This short pulse results in selective heating of the vascular lumen and immediate purpura formation but causes no substantial injury to surrounding tissue or to the overlying skin surface. The purpura that develops immediately after treatment will typically take between 10 and 14 days to resolve and is commonly replaced by a brownish discoloration that may last an additional week. This technique provides good results in treating small blood vessels, but multiple re-treatments are commonly required to produce satisfactory lightening. Although pulsed dye laser therapy initially was thought to have little risk of complications, abnormal textural changes, scar formation, and postoperative hypopigmentation have all been reported.

The copper vapor laser produces even shorter pulses of

yellow light than the flash-lamp-pumped pulsed dye laser. The copper vapor laser produces yellow light with a wavelength of 578 nm. This laser system is used in a quasi-continuous mode of operation; the individual pulses are so short—on the order of 20 nanoseconds—they appear to be emitted in continuous fashion. This laser system is unique in that it can actually produce a variable blend of yellow and green light, depending on the temperature of the elemental copper within the optical cavity. The benefit of using the extremely short pulses of light from the copper vapor laser for treating vascular lesions is that undesired thermal effects are limited by reducing the length of exposure.

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Cutaneous Aspects of Child Abuse

CHILD ABUSE continues in epidemic proportions, and all health care professionals are increasingly called on to assist in its diagnosis. Because 90% of abused children have mucocutaneous signs, dermatologists often are involved in its assessment. Bruises, sexual abuse, and burns are the foremost findings in abused children. Atypical sites for accidental trauma such as the buttocks, inner thighs, and perigenital areas should raise suspicion, as should mucosal trauma. Linear, angular, and loop-shaped injuries are highly suggestive as well. A lack of concordance between the caretaker's story and the observed injury is typical of an abuse situation.

Recent well-publicized incidents of apparent overreporting and false accusation of adults by some children have done a disservice to the urgent need for all professionals to continue to participate in the reporting process. Although parents reported without apparent culpability understandably feel victimized by child abuse laws, we as professionals must not be influenced by such protestations and must continue to look with tunnel vision at each child's potential vulnerability in every case of suspected abuse. Suspicion is the key word because every state requires us to report suspected, not proved, cases of child abuse. Can a condition such as condyloma acuminatum, always considered sexually transmitted in adults, not be considered suspicious in a toddler? Even if only 10% to 25% of cases are proved to be associated with sexual abuse, this is still a notable number of children at risk. Careful but sensitive investigation of risk factors is indicated in each case, and most cases not readily attributed to birth canal exposure require reporting.

Numerous cutaneous and mucosal disorders have occasionally been falsely attributed to child abuse: the so-called pseudo-abuse syndromes. Examples include the palpable purpura of vasculitis, southeast Asian customs such as coin rubbing and cupping, phytophotodermatitis from various plant constituents, and anogenital changes due to streptococcal infections or lichen sclerosus et atrophicus. To avoid wrongfully accusing the caretaker in these situations, expert consultation is often required. Whereas pediatricians and social workers remain paramount in managing child abuse cases, dermatologists should be increasingly involved because of their unique training in diagnosing and treating disorders of skin and mucous membranes, as well as sexually transmitted diseases.

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Oral and Topical Cyclosporine Therapy for Psoriasis

ANALOGOUS TO the discovery and development of methotrexate therapy for psoriasis, cyclosporine was first found to be an effective treatment for the psoriatic skin lesions of patients who were being studied for the drug's effect on psoriatic arthritis. In the decade since then, many investigators have reported cyclosporine efficacy in treating psoriasis when given orally, using a variety of doses ranging from 1 to 14 mg per kg of body weight per day. The results of these studies have generally shown that two thirds or more of patients have had total or substantial clearing of psoriatic lesions. With cessation of therapy, however, psoriatic lesions have recurred rapidly—within weeks.

Cyclosporine is a potent drug, and its use in organ transplant patients in high doses has produced notable adverse effects. Since psoriasis is a benign but sometimes very severe non-life threatening disease, the long-term use of cyclosporine may be limited. Clinical success in treating psoriasis has been associated with the two main side effects also seen in organ transplant patients: nephrotoxicity and hypertension. These changes are both dose-dependent and reversible, yet obviously they will limit the potential for widespread use of this drug in patients with severe or extensive psoriasis unless very low doses with minimal or negligible toxicity can be effective. Patients with severe psoriasis are now treated with phototherapy, methotrexate, or etretinate (Tegison). Another drug with an acceptable benefit to risk ratio would be welcome. For patients with mild psoriasis, there is little or no justification in using oral cyclosporine.

At the research level, the effect of cyclosporine therapy on psoriasis has reopened the question of the pathogenesis of this disease. In the past, psoriasis was not seriously considered to be an immunologically related disease. Cyclosporine has forced a re-examination of this possibility based on some of the drug's suggested mechanisms of action on immunologic systems. In the skin these include suppression of T-lymphocyte cells, interference with epidermal antigen-presenting dendritic cells, or effects on inflammatory cells. The question of whether cyclosporine may directly inhibit epidermal cell proliferation has yielded conflicting answers. Much research is needed to explore more fully the mechanisms by which cyclosporine can cause disease resolution (but not cure).

The intriguing clinical effects of oral cyclosporine have led to obvious attempts at determining whether the drug will

work by topical administration. Biren and colleagues first reported the topical effects of cyclosporine on contact dermatitis in guinea pigs. Others have subsequently shown similar effects on the skin of small animals. At least three reports have failed to show clinical effectiveness in psoriatic patients when comparing topical cyclosporine to placebo preparations. Cyclosporine was used in 2% to 5% concentrations with generic cream or ointment preparations and tested for 1 to 2 months. The lack of topical effect suggests at least three possibilities: the drug works by a systemic effect rather than locally in the skin; cyclosporine could be metabolized in part, and a metabolite might be the active agent; or adequate quantities of cyclosporine do not penetrate into the active sites of the psoriatic lesions, whether they are in the epidermis or the dermis, or both. Evidence of a local effect has recently been shown using intralesional injections of cyclosporine, with the intravenous preparation (50 mg per ml) diluted with 2 parts normal saline. After six injections over two weeks, ten of ten patients had significant improvement with a reduction in mean clinical score from 9.0 to 2.5, while placebo-injected sites had no significant improvement (9.0 to 7.9). Thus, local delivery of cyclosporine by injection directly into skin lesions can produce clinical improvement. These results will provide more impetus toward developing topical preparations and to understanding the pharmacologic effects of the drug in treating psoriasis. A successful topical preparation will allow most psoriatic patients with minimal amounts of disease to be safely treated because systemic side effects would be unlikely from limited applications.

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Oral Retinoids

In the past decade there has been a widening use of synthetic retinoids for treating various dermatologic diseases.

Isotretinoin (Accutane) continues to be indicated for and is often highly effective in treating severe nodulocystic and scarring inflammatory acne unresponsive to conventional therapy. Recently, however, isotretinoin was almost removed from the market by the Food and Drug Administration because of its teratogenicity. It is therefore essential to be fully aware of all the details of its use before initiating therapy, including careful screening of women of childbearing potential to rule out pregnancy. The manufacturer, Roche Laboratories, provides a step-by-step kit to guide physician and patient through the informed consent process to help insure patient safety. Two forms of adequate contraception are now advised for younger women taking Accutane, and careful counseling and follow-up to avoid pregnancies are essential.

Etretinate was approved in 1986 for treating severe recalcitrant psoriasis and exfoliative and generalized pustular psoriasis. In patients with recalcitrant plaque psoriasis, its optimal use is in combination with other types of treatment including phototherapy and psoralen plus ultraviolet A. Etretinate should not be used in women of childbearing age because the drug is lipid-bound and continues to be present in small but teratogenic levels for some years after discontinuation of the drug. As a result of this problem with etretinate, several clinical investigations have been conducted with the acid derivative of etretinate, known as acitretin. These studies show that acitretin has the efficacy and short-term toxicity of etretinate, but because it is more rapidly excreted, it could be considered for use in women of childbearing age with severe psoriasis providing the same care over contraception use and avoidance of pregnancy is exercised as with isotretinoin.

Other side effects of isotretinoin, etretinate, and acitretin include mucocutaneous drying, diffuse alopecia, fatigue, headaches, hepatotoxicity, lipid abnormalities, skeletal hyperostosis, pseudotumor cerebri, and myalgia.

Despite these side effects, the systemic retinoids are extremely valuable drugs that can be used in appropriately severe dermatologic diseases by physicians skilled in their use. Refinements on the basic retinoid structure are continuing to reduce the incidences of toxicity.

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Psychodermatology Update

Patients with primary psychiatric disorders who see a physician because of the mistaken belief that they have real skin disorders pose some very difficult management issues. This difficulty is intensified by the fact that, as a rule, these patients lack psychological insight and will refuse a referral to a psychiatrist. This bleak situation has been improved recently by the availability of psychopharmacologic agents that have been found to be efficacious for these psychodermatologic problems. These medications can be classified into four categories: antipsychotic, antidepressant, antianxiety, and anticompulsive.

Pimozide (Orap) is an antipsychotic medication that has been especially useful for treating persons with delusions of parasitosis, where they develop a false belief that there are insects, worms, or other imaginary ectoparasites infesting their skin. The dose used to treat this condition ranges from 1 mg to 10 mg taken orally once a day. This is a potent drug whose main side effects are extrapyramidal symptoms such as akinesia (difficulty with initiating a movement), akathisia (restlessness), and dystonia (muscle and joint stiffness). These are usually controllable with anticholinergic medications such as benztropine mesylate (Cogentin), 2 mg by mouth four times a day, or diphenhydramine hydrochloride (Benadryl), 25 mg by mouth four times a day, as needed. Tardive dyskinesia may occur with long-term use of pimozide. For older patients, patients taking high doses, or patients with preexisting cardiac abnormalities, an electrocardiogram should be done before treatment and periodically during treatment, since pimozide may prolong the QT interval. Rare cases of unexpected death have occurred in patients taking doses of about 20 mg per day.

Psychogenic excoriators often are found to produce an underlying depression or obsessive-compulsive disorder. A tricyclic antidepressant, doxepin hydrochloride (Sinequan, Adapin), is useful in treating those patients with an underlying depression. Doxepin has a notable antipruritic effect, as well as an antidepressant effect. The major side effects of doxepin are sedation, anticholinergic symptoms such as constipation, dry mouth, or urinary hesitations, and orthostatic hypotension. In elderly patients, cardiac side effects such as prolongation of the QT interval need to be monitored. Both pimozide and doxepin reduce the seizure threshold, and caution must be exercised in using them to treat patients with epilepsy.

Antianxiety agents such as alprazolam (Xanax) are helpful in managing dermatologic patients with symptoms of stress, tension, and anxiety. There are many cutaneous conditions that can be exacerbated by stress and anxiety, ranging from hyperhidrosis (excessive sweating) to psoriasis. In addition, there are self-induced skin conditions that can be exacerbated by stress and anxiety such as onychophagia (nail biting), neurodermatitis (lichen simplex chronicus), and prurigo nodularis. The usual starting dose of alprazolam ranges from 0.25 mg to 0.5 mg taken orally four times a day as needed. The short-term side effect is usually limited to sedation. Long-term use of alprazolam should be supervised by a psychiatrist. Because alprazolam was found to have a notable antidepressant effect, it is sometimes used as a substitute for an antidepressant when the cardiac and anticholinergic side effects of a tricyclic or other "classic" antidepressants pose substantial risk to the patient.

Anticompulsive agents may be useful in treating patients with obsessive-compulsive disorders seen in a dermatologic practice, such as hand eczema resulting from obsessive hand washing, trichotillomania, and acne excoriée. The prototypical medication with anticompulsive effect, clomipramine hydrochloride (Anafranil), is expected to become available in the United States in the near future.

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Preventing and Modifying the Aging Process

SKIN CHANGES in the elderly have been considered an inevitable and irreversible part of the aging process, with the undesirable texture and appearance masked with the use of cosmetics. Recently, however, there has emerged a clearer understanding that aging of the skin is the total of two processes: intrinsic changes associated with aging and extrinsic damage, particularly the accumulative effects of repeated exposure to actinic radiation, referred to as photoaging. In many instances, the cumulative actinic damage has been the major contributing factor to the changes observed in the skin of the elderly, including various degrees of wrinkling, laxity, pebbliness, roughness, leathery appearance, telangiectasias, and spotty hypo- or hyperpigmentation of the skin. This has been particularly true where exposure has been excessive, or in fair-skinned persons of Celtic background and others who have poor natural defenses against actinic radiation. The photodamaging effects on the skin also have been implicated in the development of the commonest malignant neoplasms: basal cell and squamous cell carcinomas of the skin. These malignant neoplasms are occurring in epidemic proportions.

The most damaging segment of the sun's rays has been identified as those in the ultraviolet B band of the ultraviolet light. A large number of topical sunscreening agents have been developed that if properly used will effectively screen out such rays. More recently, ultraviolet A and even rays in the infrared band also have been incriminated as contributing to the total photodamage of the skin, and some of the new sun shields have desirable ultraviolet A absorbers, as well.

Simple, effective measures have been proposed to minimize the photoaging effects of actinic radiation: avoiding sun bathing, both outdoors and in tanning parlors; wearing appropriate protective clothing when outdoors; applying sunscreen to exposed portions of the body; and choosing, whenever possible, to engage in outdoor activities before 10 AM or after 4 PM, when photodamaging rays are less intense. These measures should apply particularly to children, as mounting evidence suggests that 50% to 80% of the total accumulative photodamage occurs during the first 20 years of life. Further, it has been predicted that the regular use during childhood and adolescence of sunscreens with a sun-protective factor of 15 or greater would reduce the lifetime incidence of nonmelanoma skin cancer by as much as 70% to 80%.

Even the concept of the irreversibility of acquired photodamage is no longer tenable. It is now known that the body's own reparative mechanisms will partially correct the photodamaging aspect of the skin over a period of time if a person will remain out of the sun's harmful rays or if appropriate measures are taken to minimize exposure. Destruction and repair go on simultaneously under continued assault by actinic radiation; the balance is shifted toward repair when radiation stress is reduced.

Considerable scientific and public interest has been generated regarding the recent clinical and laboratory evidence that topically applied tretinoin (Retin-A) can accelerate the reversal of the skin damage due to excessive sun exposure and possibly intrinsic aging as well. The application of tretinoin decreases the cohesiveness of the corneocytes and promotes their shedding, so that there is a thinner, more uniform horny layer. Epidermopoiesis is enhanced, leading to a greater thickness of the epidermis with some correction of cytologic atypia, variability, and polarity. Blood flow is increased, and angiogenesis is stimulated, improving oxygenation as well as nutrient transfer to the skin. Fibroplasia is stimulated with the laying down of new collagen, leading to some improvement in skin turgor and a possible reduction of wrinkles. The accumulation of melanin granules is prevented, thus leading to a more uniform pigmentation. Finally, tretinoin has a redifferentiation, antitumor effect that causes some of the atypical cell clones of actinic keratoses to regress and disappear.

Tretinoin therapy is to be used indefinitely, starting with daily application for from eight months to a year, and then twice-weekly application thereafter. The use of tretinoin has certain drawbacks. In some patients, the changes are only slight, while in others the treatment is too irritating. Treated skin is more prone to sunburn, necessitating the use of a sunscreen.

All current information about tretinoin is still of a short-term nature, and considerable additional data will be required before its exact effectiveness and any additional side effects can be determined. For the purpose of evaluating the effects of sunlight and artificial ultraviolet radiation on the skin, a recently convened 14-member panel of the National Institutes of Health found that available evidence was insufficient to recommend the use of tretinoin and similar compounds for the treatment of sun-induced wrinkles.

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Sclerotherapy—Treating the Small Vessels

IN AMERICA the treatment of "spider" veins—vessels less than 1 mm in diameter—was pioneered by Biegeleisen, who coined the term sclerotherapy in the 1930s. Sclerotherapy is now routinely carried out by dermatologists who received training during their residencies or acquired it as postgraduates. Of patients treated, 90% are pleased with the results, and many note a reduction in leg discomfort and fatigue. Spider veins are not a purely cosmetic problem.

There is no perfect sclerosing agent. All work by initiating destruction of endothelium followed by thrombus formation and fibrosis. Sodium tetradecyl sulfate (Sotradecol) and morrhuate sodium were approved by the Food and Drug Administration decades ago during an era when such approval was easily obtained. Neither is more efficacious, and both are far more toxic than hydroxypolyethoxydodecane (Polidocanal, Aethoxysclerol), a chemical analog of xylocaine not approved by the Food and Drug Administration but widely and successfully used in Europe and Canada. Hypertonic saline also works well in treating spider and small varicose veins. Compression dressings and hosiery, which are commonly used after treating larger varicose veins and which can help reduce their recurrence, do not appear to be as important in treating most spider veins.

Side effects following treatment include streak-like pigmentation, which occurs when treatment-damaged vessels leak red blood cells into the surrounding skin. This phenomenon is not associated with the use of any one type of solution and is probably caused by vascular fragility. Tissue necrosis and ulcerations can follow treatment, particularly when sodium tetradecyl, morrhuate, and hypertonic saline are used. Extremely tiny vessels can appear in a bruise-like cloud matting, as post-treatment neovascularization, or as blush areas on the skin surrounding the treated areas. High cumulative doses of estrogen seem to intensify this phenomenon but have not produced a higher than expected incidence of more dangerous side effects. The uncommon but often unpredictable occurrence of severe and sometimes fatal side effects—deep thrombophlebitis, pulmonary emboli, and anaphylaxis—must be kept in mind. Proper patient selection, ambulation, and compression can almost eliminate these problems. It should also be remembered that there are real disadvantages when viable veins that could be used to repair an ailing heart are destroyed. To further confuse the situation, serious side effects are decidedly rarer with solutions not approved by the Food and Drug Administration, but physicians who use them may be at legal risk for doing so.

In the future, sclerotherapy may be more widely used to treat esophageal varices, hemorrhoids, and other vascular lesions. A better understanding of the etiology of spider and varicose veins may provide insights into the mechanisms of underlying diseases in which vascular growth plays a dominant role.

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Treatment of Androgenetic Alopecia

ANDROGENETIC ALOPECIA or common hereditary balding affects both men and women. The difference between the sexes is that women's hair becomes diffusely thin but they do not become bald. Thinning hair begins in the teens, 20s, and 30s in both sexes and is usually completely expressed by the age of 40. Androgenetic alopecia has a polygenic inheritance pattern and is caused by the influence of normal androgens on genetically marked scalp follicles. This results in a gradual miniaturization of affected follicles over several years. Because all the follicles are still present, it is possible to reverse this process and re-enlarge the follicles. On the other hand, involutional alopecia, or hair thinning in the later decades associated with the aging process, results in the loss of follicles, is probably not androgen-mediated, and is not expected to respond to hair growth-promoting agents.

Topical minoxidil is the first approved agent for promoting hair growth and represents a major medical advance. Though not very strong, its limited effect is real. Its successful use in androgenetic alopecia depends on careful patient selection and realistic expectations on the part of both patient and physician. Minoxidil causes partial enlargement of the miniaturized follicles, which in turn produce longer, coarser, and darker hairs—about 3 to 5 cm long. These hairs increase the coverage of the scalp.

The increase in scalp coverage produced by topical minoxidil is easily seen in men and women if the scalp is clearly visible before treatment and then is more covered, but not usually totally covered, after treatment. Men and women with androgenetic alopecia who still have adequate density to cover the scalp also respond to minoxidil, but they may not perceive the increase in partially enlarged hairs; they will primarily perceive that the hair thinning is stabilized and not progressing.

With a quantitative method of hair growth assessment that measures total hair mass in a permanently marked scalp area, studies have shown that virtually all subjects using topical minoxidil respond with some growth—with an average total weight increase of 40% in women and 46% in men. These subjects could be easily differentiated from those who were using a placebo—average total weight increase of 4% in women and 11% in men. Not all subjects perceived the increase, however. Primarily, those subjects whose scalp was visible before treatment perceived the increase in hair mass as improved coverage of their scalp.

Key factors to successful treatment with topical minoxidil

are the presence of many miniaturized hairs 1 cm long or longer and the commitment to twice daily application of the drug.

In men, topical minoxidil may be effective over the entire thinning scalp area from the frontal region to the vertex. The greater the number of miniaturized hairs, the greater the potential for success. A bald scalp, where only forehead-type vellus hair remains, will not respond satisfactorily to minoxidil. The bitemporal recession area will also not respond to the drug.

In women with androgenetic alopecia, topical minoxidil solution also produces a substantial increase in partially enlarged hairs. Women whose scalps are visible and whose hairstyles allow their scalps to show will usually enjoy the improved scalp coverage achieved. Women who already wear a wig or who expect full dense coverage may not be satisfied with the limited effect of topical minoxidil, however.

Topical minoxidil is easy to use and appears to be completely safe in those with a normal cardiovascular state. Side effects consist mainly of skin irritation in a small number of patients, some of whom become allergic to the drug or to the propylene glycol in the vehicle.

Treatment with topical minoxidil must be continued indefinitely in androgenetic alopecia; otherwise, normal heredity takes over. Hence the expense of the drug must be considered before starting its use. If treatment is stopped, the newly stimulated growth is lost within one to two months. Not all patients maintain the initial level of hair growth even with continued treatment.

Topical minoxidil, with its real albeit limited effects, has ushered in a new era of hair growth-promoting agents by showing that reversal of androgenetic alopecia is achievable. It has greatly stimulated hair research, and in the future many other new treatments can be expected for this normal but unpopular hereditary trait.

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Using Cultured Keratinocytes for Treating Burns

THE IDEA OF USING keratinocyte cultures as skin grafts was first promoted nearly 40 years ago and was based on observations that keratinocytes grew out from pieces of human skin in explant culture in multilayered sheets reminiscent of epidermis. It is this ability of cultured keratinocytes to form an epidermis-like organ in vitro that allows the transfer of the cell sheets to recipients as epidermal allografts. Large-scale keratinocyte culture became feasible with advances in technology developed by Green and associates in 1975. The power of this technique to provide large amounts of autologous epidermis that would otherwise not be available was dramatically shown in 1984 when the Green group treated two pediatric burn patients with grafted cultured keratinocytes covering 49% and 54% of their body surface area. In full-thickness burns, spontaneous re-epithelialization is not possible because skin adnexal structures are destroyed. The sources of conventional autograft skin are limited in severely burned patients by the lack of uninjured donor sites. Modern keratinocyte culture methods can generate enough epidermis in vitro to graft an adult's entire body surface area within three to four weeks.

Unfortunately, keratinocyte cultures alone replace only the epidermis; in full-thickness burns, the dermis is also lost. The long-term morbidity of major burn injury is primarily due to the scarring and contractures that result from damage to or loss of the dermis. For this reason, efforts to develop more comprehensive synthetic skin grafts that replace both the epidermis and the dermis have begun. The first such composite skin graft used to treat burns was developed by Cuono and colleagues in 1986. In this graft, allogeneic cadaveric dermis is engrafted and provides support for autologous keratinocyte cultures that provide the new epidermis. The reconstituted skin of this composite graft includes functional melanocytes and Langerhans cells in the epidermis. The dermal-epidermal junction, including anchoring fibrils, is fully reconstituted within weeks of graft placement. Three-year follow-up data indicate that this method results in a durable skin replacement with notably less scarring than would be expected from conventional grafting techniques. Analysis by DNA "fingerprinting" of engrafted cadaveric dermis indicates that allogeneic cells are largely replaced or absent within weeks of engraftment, although classic graft rejection is (fortunately) not observed. This composite method may be possible in severe burn patients because of the profound immunosuppression that accompanies the burn injury.

In 1983 Hefton and colleagues reported successful engraftment of allogeneic keratinocyte cultures onto burn patients. The use of such allogeneic cultures to treat serious burns would be advantageous because graftable tissue would be readily available in potentially limitless quantities. More recent evidence suggests that in partial thickness wounds in immunocompetent patients, allogeneic cultures may not be permanent but rather are gradually displaced by autologous keratinocytes from subjacent epidermal adnexae. As yet we do not know whether cultured allografts would persist if autologous epidermal elements are far removed from the graft site, as is the case in extensive full-thickness burns.

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Surgical Margins for Melanoma

THE QUESTION OF how wide a surgical margin is necessary when excising a melanoma less than 2 mm in thickness now appears to have been answered. The World Health Organization Melanoma Group designed a randomized prospective study with a large number of patients (703) that clearly shows that excisions with 1-cm cutaneous margins were as safe as wide excision margins (3 cm or more) in melanomas no

thicker than 2 mm (excluding those on the face, hands, or feet). The operative treatment in both groups of patients studied did include an additional 1 cm of subcutaneous tissue beyond the cutaneous margins. This study puts to rest the traditional dogma that wide excision is beneficial for all melanomas. Since most melanomas that are diagnosed today are less than 2 mm in thickness, this should change the treatment for many melanoma patients and the thinking that wide surgical margins decrease local recurrence rates and somehow increase survival rates in all melanoma patients.

The real question that now remains regarding surgical margins and melanomas greater than 2 mm thick is what excision margin is necessary to prevent local recurrences, even if survival rates are not really affected. Results from the best studies reported to date from the World Health Organization (WHO) (593 patients) and the New York University-Massachusetts General Hospital (NYU-MGH) Clinical Cooperative Group (598 patients) did not show a decreased rate of local recurrences with surgical margins greater than 3.0 cm. In the WHO study, an increase in the local recurrence rate was found only when surgical margins were less than 2.0 cm, while in the NYU-MGH study only surgical margins less than 1.5 cm led to higher recurrence rates. It appears that the frequency of local recurrence is related more to tumor thickness than to the width of the surgical margin. Until a prospective randomized study is done of thicker melanomas, the minimal safe surgical margin cannot be really recommended. Margins greater than 3 cm may be unnecessary, however. A 2.0 cm surgical margin is probably the minimum that should be attempted without increasing the possibility of local recurrences.

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Editorials

A Higher Duty

We live in a biologic world of predators and prey. It is nature's way. It is a matter of instinct and reality. Humans are not immune to preying upon others or themselves being prey. It is a competitive world. Success in this biologic world tends to come to those who can best take advantage of weakness. Civilization has progressed slowly and, we like to believe, inexorably. But the veneer of civilization is still very thin. The stronger tend to succeed and the weaker tend to succumb. This will probably never change and probably never should change, since it is rooted in the biologic nature of human society and the world as it is.

Medicine, at least in the ancient Hippocratic tradition and probably long before that, called physicians to something of a higher duty, that is, to care for the weak and afflicted, to try to postpone their death, and, if possible, to help restore their health and usefulness. It has been a profession where skills and knowledge are learned and used in the service of fellow humans who needed help. But physicians themselves have always been humans, and throughout all history, there have been some who preyed upon their patients and were suspected or known to take advantage of them, often for economic gain. So the fact that there are now predators in health care who prey upon the weak is really not new. The principal difference now is that the major predators are less apt to be personal physicians caring for their patients and much more likely to be third parties who, encouraged by society through government and business initiatives and armed with newly found fiscal strength because they pay most of the bills, are finding their prey in the relatively weakened position of physicians and patients in the business enterprise that health care has recently become.

Physicians like to think of medicine as a noble profession. What does a noble profession do when it finds itself and those it serves being preyed upon by stronger third parties who seem to hold most of the power? Its tradition is one of service, rather than one of individual or professional gain, yet it is being swept, almost as a matter of survival, into a new arena of predators and prey in health care. Neither the law, medicine, education, nor even some of the professionals of the cloth—all traditionally considered to be among the learned professions—have been immune to the temptation, or perhaps sometimes necessity, to begin to substitute gain for service in their professional activities. But when this occurs, to what extent is it good for the professions or for their always relatively weaker clients, the patients or the public they serve?

Is there a higher duty for these professions? It hardly can be denied that in its essence this is truly a biologic world of predators and prey, but there is something new. As we advance toward what we call civilization, predators and prey are becoming more interdependent, socially as well as biologically. The veneer of civilization still remains very thin, but the new interdependence among predators and prey is very real. Illness in the work force or in the families of workers affects employers adversely, and a national government needs a healthy and well-educated citizenry if a nation is to compete successfully in the social, economic, and political world as it is today. Physicians and the medical profession are placed at many of the interfaces where the predators and prey in today's society interact and leave their human victims of injury, illness, and human waste, who then often need professional health care.

It would seem, therefore, that there may be a higher duty for physicians and the medical profession in these times. Physicians are in the front lines where the human struggle to balance predators and prey is joined. Medicine and the medical profession are among those in the forefront of the civilized effort to protect the weak. In today's social, economic, and political system of health care, as it is in this nation, physicians and the patients they care for are the ones who are the weak, and who are therefore the prey. Civilization calls for some controls over predators and their always relatively helpless prey. To foster this restraint on predators is a higher duty of civilized persons everywhere, and some might say that it is a higher or even a highest duty of any who follow a profession dedicated to the care of the sick and afflicted, who are therefore weak, and to its corollary, the promotion of human health in all its present day ramifications. The route to this higher duty lies in the professional tradition of selfless and persistent advocacy of the weak, who are the sick and afflicted patients of physicians, and the health care public, both relatively powerless and without genuine professional advocates in the present day power structure of health care in this nation.

MSMW

What Does Seropositivity for HTLV-I Mean?

The spectrum of human T-cell lymphotropic virus (HTLV-I)-related disease remains incompletely defined but includes adult T-cell leukemia and chronic myelopathy. Of patients in some areas of Japan, Jamaica, Trinidad, and Tobago with newly diagnosed adult non-Hodgkin's lymphoma, 40% to 60% have evidence of HTLV-I infection. In Japan 96% to 98% of infected persons apparently remain asymptomatic but serve as a reservoir for further transmission of the virus.[1]

Interest in HTLV-I has increased in the United States, with reports of clusters of HTLV-I-infected persons in the southeastern United States at rates similar to those reported for Caribbean blacks but at a lower rate than that observed in southwestern Japan.[2] More recently a serologic evaluation of 214 persons in New Orleans with histories of intravenous drug use showed an astounding seroprevalence rate for HTLV-I of 49.3%.[3] Our own unpublished data from the University of South Alabama Medical Center show a seroprevalence rate of 3.7% in unselected emergency department patients using the enzyme-linked immunosorbent assay (ELISA) technology presently available. On the basis of these data, we and others have begun to evaluate the clinical implications of infection with HTLV-I.[4]

Several recent developments have forced a major reconsideration of our approach to this problem, however. It has been clear that neither the ELISA, radioimmunoprecipitation assay (RIPA), nor blotting techniques available for HTLV-I testing have the capacity to discriminate between HTLV-I and the related retrovirus, HTLV-II.[5] Two groups

recently have noted that those persons in the United States who are seropositive for HTLV-I are, in many cases, actually infected with HTLV-II, not HTLV-I.

In a study of 20 HTLV-I-seropositive persons from New Orleans, Newark, New Jersey, and Miami using the polymerase chain reaction (PCR), Gore and colleagues reported that 15 (75%) were infected with HTLV-II, 2 (10%) with HTLV-I, and 3 (15%) were coinfected with HTLV-I and HTLV-II.[6] Another study of 16 intravenous drug users from New Orleans who tested seropositive for HTLV-I by either immunoblot or RIPA confirmation reported that 14 (89%) were infected with HTLV-II using the PCR technique, with only 2 patients infected with HTLV-I.[7] Interestingly, there is little evidence that homosexual populations in the United States who are at high risk for infection with the human immunodeficiency virus (HIV) are coinfected with either HTLV-I or HTLV-II.[8] This appears not to be the case in other areas of the world, including Trinidad and Brazil.[1,9,10] Otherwise, there have been few definitive reports of HTLV-II infection, and no region endemic for this virus has been identified. Two cases of hairy cell leukemia and a single case of pancytopenia have been attributed to HTLV-II infection. Infected populations other than intravenous drug users have not been defined.

The excellent review article by Dixon and co-workers elsewhere in this issue is a logical place to start in the understanding of the problem of HTLV-I infection. The entire area of HTLV-I and HTLV-II infection in the United States and the Caribbean, however, requires reassessment using new technologies that allow a clear distinction between infected populations.

Despite the controversies and uncertainties, physicians will be called on to counsel those who test positive for HTLV-I. Based on what is known about transmission, seropositive persons should be counseled not to donate blood or to share needles. Pregnant women should be discouraged from breast-feeding their infants.[11] The Centers for Disease Control have noted that "the paucity of data concerning sexual transmission of HTLV-I/HTLV-II does not permit a firm recommendation concerning sex practices" to infected persons.[5(p745)] The presence of a substantial number of persons infected with HTLV-I and HTLV-II in the United States and the lack of information about transmission and the natural history of infection require that extensive investigation of this problem be initiated.

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Bone Marrow Transplantation

THE READERS of this and the next issue of the journal have been provided with a lucid, balanced, and up-to-date review of bone marrow transplantation by Chao and Blume. One of the leaders in this field, Dr Blume started a highly successful bone marrow transplantation program at the City of Hope Medical Center (Duarte, Calif) 15 years ago. He brings us the perspective of a clinical investigator who has seen bone marrow transplantation develop as a treatment modality, almost from its inception.

In the 1970s marrow transplantation, pioneered by E. Donnell Thomas in Seattle, was widely regarded as an experimental procedure with scant promise, although an unbiased examination of even the early results clearly showed otherwise. Transplantation was thought to have so little potential that in 1971 Dr Thomas's program was almost closed for want of university support, and administrators at Duarte made the ill-advised decision to discontinue Dr Blume's program in 1977. Even in 1980, when the superiority of using marrow transplantation to treat patients in first remission seemed quite clear, an editorial in the *Annals of Internal Medicine* proclaimed:

> Thus, although a prospective controlled trial in young patients with acute nonlymphocytic leukemia in first remission comparing transplantation with intensive consolidation and maintenance such as used by Preisler and associates would be of interest, the routine use of marrow transplantation is not indicated at present.[1]

How the situation has changed! New transplantation programs have appeared at an astonishing rate. Many of them are achieving excellent results, and there is no doubt that bone marrow transplantation has "arrived."

Why has this happened? Have there been such rapid strides in the technology of transplantation that an unripe technology may now be deemed to have advanced to the point where patients can benefit from it? Not so. Chao and Blume quite properly characterize progress as "slow and cumbersome." When Blume and colleagues[2,3] and Thomas and coworkers[4] first did allogeneic transplantations in patients with acute myelogenous leukemia in complete remission, the apparent cure rate was in the range of 50% to 60%. There has been little or no change in these figures in the intervening decade, although we hope that advances such as the introduction of acyclovir for treating herpes zoster infections and ganciclovir and immunoglobulin for treating cytomegalovirus infections, better protocols for preventing graft-versus-host disease, and the development of more potent preparatory regimens will gradually result in some improvement in the rate of long-term survival. When Thomas, Blume, and their associates were achieving cure rates of over 50%, chemotherapy alone yielded rates of less than 10%, although slightly higher figures were claimed by some. Yet, quite unaccountably, most physicians at the time regarded the use of

bone marrow transplantation as only a desperate, last-ditch measure in managing patients with acute leukemia. Although there has been some improvement in the results obtained by marrow transplantation, encouraging strides have also been made in developing new chemotherapeutic programs for treating acute myeloid leukemia. Impressive cure rates have been reported in adult leukemia patients treated with high-dose cytosine arabinoside.[5] These results need to be confirmed, and I do not suggest that bone marrow transplantation is passé in the treatment of acute leukemia in first remission. It is ironic, however, that now that it is readily accepted by the profession, the case for transplantation is somewhat less clear-cut than it was 15 years ago.

One of the major surprises in the area of bone marrow transplantation has been the success that has attended the use of autologous transplantation, particularly in the therapy for acute leukemia. It did not seem likely that removing marrow from a body that had the seeds of relapse and re-infusing it would accomplish much for a patient. Yet, as Chao and Blume point out in the next issue of the journal, promising results are being observed at several centers, with a 35% to 50% chance of disease-free survival in patients who are in the first remission of acute myelogenous leukemia. We have now done this procedure on a number of patients at Scripps Clinic with similar results.

One of the potentially exciting advances highlighted by Chao and Blume is using autologous peripheral blood stem cells for transplantation. As yet, the technique is cumbersome, requiring repeated apheresis. But this is a problem that might well be overcome in the not-too-distant future. As an ever-increasing number of cytokines are identified and cloned, the expansion of a small population of hematopoietic stem cells in vitro may soon be within our grasp. In nature there is little need for stem cells to proliferate, since their progeny have the capability of undergoing the repeated divisions required to supply the blood stream with its rapidly-turning-over formed elements. But the very fact that the marrow can be reconstituted by transplantation shows that stem cells do have the capacity to increase their own numbers.

Who would not give a marrow sample to save his or her own life? While autologous donors will always be readily available, the same is not always true in the case of allogeneic donation, particularly from an unrelated donor. It is a remarkable tribute to the altruism that exists in our society that there are those willing to undergo general anesthesia and multiple marrow punctures to help someone they have never even met. But one can hardly expect such good Samaritans to be in unlimited supply. Thus, the use of peripheral blood stem cells has even greater potential application to allogeneic transplantation than it does to autologous donation. How much easier it would be if we could merely draw a small sample of blood from a willing donor. We could then harvest the multi-potential stem cells and feed them interleukin-3 and whatever other cytokines are required to expand them by six or seven orders of magnitude. The ability to expand a stem cell population would also make it more feasible to introduce into the parent population genes for drug resistance. Such genes could make it possible to treat a patient with chemotherapy that would not be tolerated otherwise.

Bone marrow transplantation has become respectable but not, ironically, because its lead over alternative technologies has widened—that has narrowed. Rather, physicians gradually seem to have begun to understand and accept the earlier data that showed how much the procedure could accomplish for patients. The potential exists for great advances in this technology over the next few years. We can even dream of the time that a blood sample of 10 ml is all that is needed for transplantation to be done successfully. At the same time, we can continue to hope for a "magic bullet" that cures many of the diseases that are now successfully treated by transplantation.

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Case Reports

Acute Oleander Poisoning

A Suicide Attempt in a Geriatric Patient

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THE COMMON OLEANDER PLANT is one of several families of plants that have been shown to contain nondigitalis cardiac glycosides. Oleander is an idiom for plants of the *Nerium oleander* L, *Nerium indicum,* and *Nerium odorum* species. Common names include soland, lorier bol, rosebay, and rose laurel. These plants are widely distributed throughout the tropical to the subtemperate zones of the world and in the United States are frequently found from South Carolina west to California and points south. Their decorative flowers and prolific growth make them popular shrubs for landscaping. They also may be found growing wild.[1]

The oleander's widespread prevalence and alluring flowers make it a particular hazard for accidental ingestion by small children, and most documented cases of human poisoning by this plant have occurred in the pediatric population.[1] The plant also has shown toxicologic importance for accidents when used in folk medicines when adults unknowingly eat parts of the plant or food that has come into contact with the plant, such as hot-dog sticks, and in homicides or suicides. Also, as our case illustrates, toxicities are not limited to temperate climates.[2]

All parts of the plant contain cardiac glycosides, including the roots and the smoke produced from burning, as heat does not inactivate the glycosides. The major toxic effects are similar to those of a digitalis overdose. This includes direct glycoside poisoning of the sodium-potassium pump of the heart and increased vagotonia. Most symptoms from oleander poisoning are cardiac and gastrointestinal in nature. Central nervous system disturbances and death may follow.[1-4]

We report a case of intentional oleander ingestion by a nursing home patient after she allegedly received the oleander plant from a mail-order service she located through an advertisement in a periodical.

Report of a Case

The patient, an 83-year-old resident of a nursing home, was discovered on the morning of admission to be combative and semilucid. A mug with a small amount of brownish material was found at the patient's bedside, and an ingestion of some type was suspected. On arrival in the emergency department, the patient reported that she had drunk oleander tea the night before. Her medical history included severe osteoporosis, degenerative osteoarthritis, arteriosclerotic heart disease, and overflow incontinence of the bladder, for which she was taking naproxen sodium 500 mg twice a day, trazodone hydrochloride 50 mg at bedtime, triazolam 0.125 mg at bedtime, calcium carbonate, and conjugated estrogen daily. She had experienced no decline in her mental faculties, and her admission to the nursing home was purely on the basis of her physical debility. She had no known allergies.

On initial examination, the patient's blood pressure was 102/50 mm of mercury, with a pulse rate of 40 per minute. Her mental status alternated between periods of combativeness and semilucidity. Examination of her head, eyes, ears, nose, and throat revealed pupils that were equal and reactive to light and accommodation. Her extraocular motor muscles were intact. Her chest and lungs were clear to auscultation and percussion. Cardiovascular examination showed an irregular rhythm, with a grade 3/6 holosystolic murmur heard over the left sternal border. On abdominal examination there was no hepatosplenomegaly, and bowel sounds were active. Deep tendon reflexes were 2+ and equal.

In the emergency department, a cardiac monitor strip revealed no apparent atrial activity, with a ventricular rate of 35 to 45. The QRS interval was 0.138 seconds. The patient was given 0.5 mg of intravenous atropine sulfate, which resolved her bradycardia. Atropine at the same dosage was given twice during the first several hours of her hospital stay because her bradycardia recurred. Her mental status did not improve with the resolution of her bradycardia. A 12-lead electrocardiogram after atropine had been given showed atrial fibrillation with nonspecific ST segment changes and intraventricular conduction delay. The patient was given activated charcoal in a 70% sorbitol slurry and appropriate intravenous fluids and was admitted to the intensive care unit. Initial laboratory studies revealed a serum sodium level of 121 mmol per liter (mEq per liter), a potassium of 6.1 mmol per liter (mEq per liter), and a digoxin concentration of 7.1 ng per ml.

For the next 36 hours, the patient's condition remained stable, and she had a gradual resolution of her hyponatremia, hyperkalemia, and elevated digoxin levels (Table 1). On the third day of her hospital stay, she was transferred to the psychiatric unit, where she gradually became more conversant, calmer, and was able to address her concerns about autonomy and dignity during the waning years of her life. She was then discharged from the hospital to a different nursing home.

Discussion

Several families of plants, including foxglove and oleander, have been identified as containing cardiac glycosides. These glycosides may include oleandrin, oleandroside, nerioside, digitoxigenin, thevetin, and thevetoxin.[2,4] Although some of these glycosides have therapeutic properties—William Withering, in his classic account from 1795, described treating dropsy with foxglove—exposure to these plants in toxic amounts may induce cardiotoxic effects as well as gastrointestinal symptoms. The cardiac glycosides in oleander produce more gastrointestinal effects than those in digoxin, and the symptoms range from nausea and vomiting to cramping and bloody diarrhea. In addition, oleander may

(Driggers DA, Solbrig R, Steiner JF, et al: Acute oleander poisoning—A suicide attempt in a geriatric patient. West J Med 1989 Dec; 151:660-662)

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TABLE 1.—*Laboratory Values in an 83-Year-Old Woman With Possible Oleander Poisoning*

	Day 1				Day 2	Day 3		Day 6
	Time							
Laboratory Measurements	*0810*	*1355*	*1605*	*2015*	*0535*	*0650*	*2040*	*0650*
Sodium, mmol/liter	121.0	124.0	119.0	123.0	123.0	126.0	130.0	136.0
Potassium, mmol/liter	6.1	5.6	4.4	4.3	3.4	3.9	3.5	4.1
Digoxin, ng/ml	>7.1	4.6	.....	3.5	1.8	0.8	1.1	Not drawn

cause irritation to the mucosal membranes, resulting in burning around the mouth and increased salivation. Confusion, dizziness, drowsiness, weakness, visual disturbances, and mydriasis are central nervous system manifestations of toxicity.[2,3,5,6]

The most serious side effects of oleander poisoning are cardiac. Various ventricular dysrhythmias and tachyarrhythmias have been described. Bradycardia and heart block are the most frequently reported cardiac abnormalities.[1,3-5,7-9] Electrocardiography often reveals an increased PR interval, a decreased QRS-T interval, and T wave flattening or inversion.[4] One investigator described anterolateral wall ischemic changes in a 22-year-old.[8] It is thought that these clinical manifestations are the result of both increased vagotonia and direct cardiac glycoside toxicity.[2,6] An interesting primary effect of the digitalis is the disruption of the normal sodium-potassium adenosine triphosphatase (ATPase) activity within the cell membrane.[2,3,6] If we assume a similar phenomenon with glycosides found in oleander leaves, this toxicity should manifest itself by an elevation in the serum potassium level and a depression in the serum sodium level, as noted in our patient. Insulin and glucose infusion to correct the hyperkalemia may be less effective because of the disruption of the ATPase-dependent pump.[4]

The treatment of oleander poisoning is empirically based on the treatment of digitalis-glycoside toxicity and consists of supporting the patient hemodynamically. This may include administering atropine for severe bradycardia; using phenytoin or lidocaine hydrochloride to control dysrhythmias; placing a temporary venous pacemaker; or electrical countershock.[4,6,10] Although not tested in humans, dipotassium edetate, a calcium chelating agent, has been shown to be successful in treating oleander overdose in cats.[11]

Administering digoxin-specific Fab antibody fragments (Digibind) also has been advocated.[3] In our patient, Digibind therapy was held in reserve because of her rapid recovery and our lack of adequate clinical experience using this substance. The only report on the use of digoxin-specific Fab antibody for oleander poisoning was in a patient with a digoxin level of 1.5 ng per ml and irregular bradycardia.[3] It must be remembered that the digoxin level indicates an unknown portion of the total glycosides[2,9] and that Digibind binds with an unknown portion of the total glycosides. The use of digoxin-specific antibodies prevents further monitoring with digoxin levels.[3]

Other treatment methods are aimed at removing the toxic substance from the stomach by emesis. Special concern must be given to a patient with bradycardia before emesis is induced because of the possibility of a vagal reaction and worsening of the bradycardia.

Unabsorbed glycosides may be bound to some extent, depending on the particular glycoside, by various binding agents in the gut. These agents theoretically should be more effective in absorbing less polar glycosides, such as digitoxin, than the more polar glycosides like digoxin (for example, cholestyramine resin and colestipol). The use of these agents is not thought to have substantial value in the treatment of advanced toxicity, and they were not used in our patient.[12] Dialysis has also been shown to be of little benefit in ameliorating digitalis toxicity.[9,10]

Activated charcoal has been shown to be useful in preventing further absorption of the cardiac glycosides and was used. In these circumstances, activated charcoal is most effective when used soon after ingestion of the toxin; however, it also may be of therapeutic benefit by its interruption of the enterohepatic circulation of the glycoside. Unfortunately, not all glycosides are involved in the enterohepatic circulation sufficiently to be affected by intermittent charcoal therapy.[12] It is unknown if the glycosides of oleander have enterohepatic circulation, but administering activated charcoal is usually without risk and may be beneficial.

The cross-reactivity seen between digoxin radioimmunoassays and the glycosides of oleander is well known.[2] This cross-reactivity can at least identify the presence of a cardioactive glycoside in the case of an unknown poisoning. Beyond its qualitative usefulness in oleander toxicity, however, the digoxin serum level's clinical significance is unknown. The digoxin radioimmunoassay is not specific for all of the glycosides that may be present in the oleander plant. Cheung and co-workers report radioimmunoassay results on known aliquots of *N oleander* (white, pink oleander) and *N thevetia peruviana* (yellow oleander) mixed in pooled, drug-free human serum. These results indicate that relatively low serum concentrations—2 grams of leaf extract diluted 2,560- to 128,000-fold—give serum levels of 0.5 to 3 ng per ml.[9] This correlates with reports of death after ingestion of one or two leaves or one seed.[1,3,6,9,13]

In a previous report, a fatal case of oleander overdose was documented with an apparent digoxin level of 1.2 ng per ml and a postmortem level of 6.4 ng per ml.[4] The authors speculated that this may be because of postmortem redistribution of the drug and a difference in cross-reactivity with oleander for the two assays used. Our patient survived with a level of 7.1 ng per ml measured using the radioimmunoassay technique of the Mayo Clinic laboratory. There appears to be a linear relationship established for the digoxin serum level (natural log) and time, with a half-life of approximately 13 hours (Figure 1). It is unknown exactly what is being measured, however, and because the amount of cross-reactivity is unknown, the use of a digoxin radioimmunoassay in oleander toxicity will only indicate the presence of glycoside and may not indicate the degree of toxicity.

It is interesting that our patient's mental state did improve as the assayed digoxin serum level declined. A digitalis overdose can cause delirium, but whether this is due to serum hyponatremia and central nervous system intracellular hy-

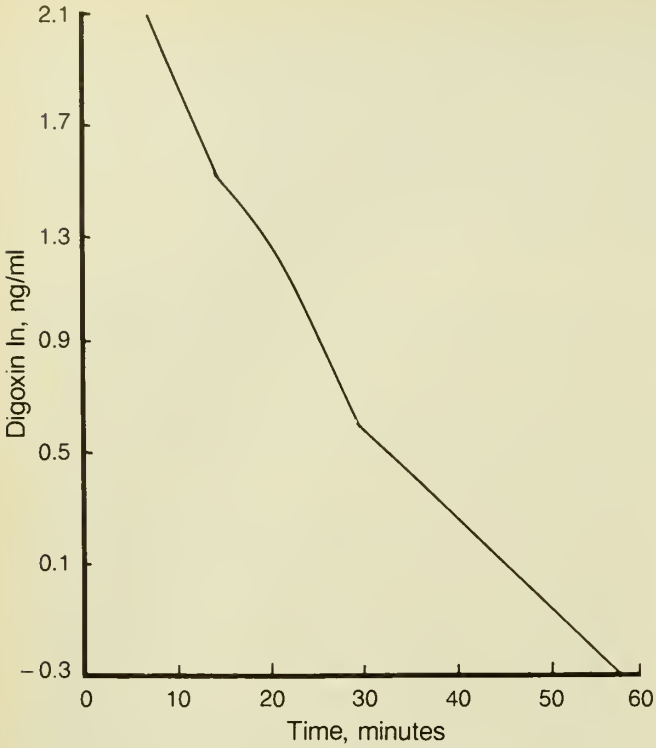

Figure 1.—Digoxin serum concentration versus time, in minutes, is shown.

pernatremia is unknown. Using the crude cross-reactivity figures mentioned by Osterloh and colleagues, our patient had a serum level of approximately 700 ng per ml of cardenolides.[2] Their 96-year-old patient had a much lower level and succeeded in her suicide attempt. Her sodium level was high at 161 mmol per liter and her hyperkalemia worse at a potassium level of 8.3 mmol per liter. Why our patient survived is unknown. Differences in age, organ system health, oleander species, and in poison preparation are all possibilities.

The social aspects of this case are probably more important than the medical. Specifically, oleander is grown throughout the warm climates of the United States, with large sections of highway medians in California planted with it. Knowledgeable members of the geriatric population realize that oleander poisoning can be fatal with relatively small amounts ingested. Osterloh and associates calculated the lethal oleander leaf dose of their patient at approximately 4 grams.[2] Practicing physicians need to understand the potential lethal properties of oleander and its availability throughout the country. This is especially the case for geriatric patients because the suicide rate in those older than 65 years is higher than in any other age group and is projected to increase.[14]

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Cardiac Rupture in Blunt Trauma Without External Signs of Chest Injury

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SURVIVORS OF CARDIAC RUPTURE due to blunt trauma are rare. There are often massive associated injuries, and diagnosis may be difficult. On the other hand, patients at first may have minimal or no signs of chest injury, yet suffer from cardiac rupture. Two such patients are described.

Reports of Cases

Case 1

A 23-year-old woman lost control of her car and struck a tree. At the scene of the accident, she was hypotensive (blood pressure 80/50 mm of mercury), and this gradually progressed to a blood pressure of 60 mm of mercury palpable on arrival at the emergency department. Examination showed a mandibular fracture and notable soft tissue swelling in the neck. She had no bruises or other evidence of chest or abdominal trauma. A chest radiograph showed no rib fractures or other obvious signs of injury. Following nasotracheal intubation and crystalloid infusion, her hypotension persisted. On peritoneal lavage, no abnormalities were detected. Her urine output was minimal. Her neck veins showed progressive distention, and an emergency echocardiogram showed pericardial tamponade. A pericardiocentesis was done before a surgical procedure. Removing 100 ml of nonclotted blood from the pericardial sac improved the patient's systolic blood pressure to 80 mm of mercury. In the operating room, a median sternotomy was done, and a tense, blue, bulging pericardium was noted. This was incised, with immediate evacuation of blood, and the systolic blood pressure rose to 140 mm of mercury. A perforation of the right atrial appendage was found and controlled using a fingertip. This tear was then easily oversewn. No other associated injuries were identified. The patient had an uneventful convalescence and was dismissed on the sixth postoperative day to be admitted later for definitive oral surgery for the mandibular fracture.

Case 2

The patient, a 50-year-old woman, was involved in a single-vehicle car accident in which she was pinned under the

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car and required extraction. She was hypotensive but alert on arrival at the emergency department, with a blood pressure of 60 mm of mercury palpable. She reported having upper abdominal pain. She did not have neck vein distention, and there was no external evidence of chest or abdominal trauma. She had an open fracture of the left patella and multiple facial lacerations as her only other associated injuries. A chest radiograph showed a collapsed right lung with fluid in the right chest. A chest tube was inserted, with an immediate return of a large amount of blood. She was taken to the operating room for an emergency right thoracotomy, where the bleeding was found to be coming from a small tear in the pericardium adjacent to the superior vena cava. The pericardium was opened, and a tear in the right atrial appendage was identified as the source of bleeding. This was easily controlled using a fingertip and then oversewn, which stopped her bleeding completely. There were no associated intrathoracic injuries identified. The patient's hospital course was somewhat prolonged by her orthopedic injuries, but no other associated abdominal or thoracic complications developed.

Discussion

Several factors bear emphasis regarding these two patients. In both, there was no external evidence of chest injury. Freeark has stressed the concept of "blunt torso trauma," emphasizing the possibility of intrathoracic injuries when abdominal trauma predominates, and vice versa.[1] These cases corroborate this concept. The mechanism of rupture is not known, but the location of the tears in the thin wall of the right atrial appendage suggests the possibility of a shock wave transmitted from the torso to a tensely filled atrium just before atrial contraction.

The clinical characteristics of these two patients differed because of the status of their pericardiums. If the pericardium is intact, cardiac rupture results in tamponade, with neck vein distention, hypotension, and no sign of bleeding. If the pericardium is torn, the blood has egress into the pleural cavity, and hemorrhage dominates the clinical picture. An intact pericardium could also be associated with mixed features of tamponade and hypovolemic shock from other injuries, so assessing the intravascular volume status is crucial.

A review of the available literature on blunt atrial injuries elicits a relative paucity of cases. In their excellent review, Patton and co-workers reported three cases of blunt atrial tears, two involving the left atrium and one involving the right atrium.[2] In all three of these patients, however, there were obvious signs of chest injury. Two patients had anterior chest contusions, and the other had a flail sternum. In their review of 21 other cases reported in the literature, these authors identified a syndrome including high-speed automobile accidents and substantial evidence of chest trauma associated with hypotension and mental aberrations such as confusion or coma. They also noted the rather surprising length of time that could pass between an accident and treatment, ranging from 30 minutes to 9 hours.

Echocardiography has been used in penetrating and blunt abdominal trauma to diagnose not only intracardiac defects but also to establish the presence of a tamponade when the pericardium is intact. Whye and colleagues reviewed the use of echocardiography in cases of penetrating cardiac trauma and suggested that the increasing availability of portable echocardiography units should make this an examination of increasing use in emergency departments.[3]

The ubiquity and severity of thoracic trauma were highlighted by Estrera and Schreiber, who noted that approximately 165,000 people die of traumatic causes each year and that thoracic trauma accounts for 25% of these deaths, with primary cardiac injury as a major contributing cause.[4] They emphasized that every member of a trauma team should have a thorough knowledge of the diagnosis and management of cardiac injury, both penetrating and blunt, to effect an improvement in the overall survival rate of this group of patients.

The two cases here presented take this appeal one step further. Cardiac injuries including atrial disruption should be considered not only when there is obvious evidence of thoracic trauma but in any patient who has suffered severe blunt torso trauma, even in the absence of overt signs of chest trauma. Because treatment is relatively simple and effective if instituted in time, emphasis should be placed on diagnosis.

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Fatal Intraoperative Disseminated Intravascular Coagulation

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DISSEMINATED INTRAVASCULAR COAGULATION (DIC) is an uncommon intraoperative event. It usually occurs as a complication of malignant disease, infection, or trauma or in association with liver, collagen, or vascular disease.[1-3] It has also been described in pregnant patients.[3,4] When it does occur intraoperatively, DIC is usually mild and can be corrected by administering coagulation factors. Severe DIC is rare and generally regarded as an "incidental preterminal event occurring in a variety of acute catastrophic illnesses."[5] Although the intraoperative occurrence of severe DIC has been reported,[6-8] fulminant intraoperative DIC has not previously been described in patients who are not acutely ill or undergoing procedures such as cardiopulmonary bypass—procedures that in themselves increase the risk of DIC. We report a case of severe, fulminant, disseminated intravascular coagulation occurring during elective cholecystectomy and colostomy revision.

Report of a Case

A 66-year-old woman weighing 85 kg (187 lb), who had a history of chronic cholelithiasis and was having more frequent episodes of fatty food intolerance and intermittent jaundice, was scheduled for an elective cholecystectomy and revision of her colostomy. The patient had undergone a low

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anterior resection for cancer of the colon five years before. There was no evidence of tumor recurrence. She had a coronary artery bypass operation two years before this admission and was free of cardiac symptoms. Other medical problems included mild renal insufficiency and glaucoma. Her current medications included diltiazem hydrochloride, propranolol hydrochloride, and methazolamide. Besides obesity and the absence of peripheral pulses, her physical examination findings were normal. Preoperative laboratory study findings are summarized in Table 1. The electrocardiogram revealed evidence of an old inferior myocardial infarction and flattened T waves. The patient was given a bowel preparation of neomycin sulphate and erythromycin the day before her surgical procedure. The morning of her operation she received cefoxitin sodium intravenously.

Following preoxygenation, general anesthesia was induced intravenously with fentanyl citrate, lidocaine hydrochloride, and sodium thiopental. Succinylcholine chloride was used to facilitate endotracheal intubation. Monitors used included an esophageal stethoscope, a temperature probe, an automated blood pressure cuff, electrocardiography, and a pulse oximeter. Anesthesia was maintained using isoflurane, nitrous oxide, and oxygen. At laparotomy the gallbladder appeared inflamed. There was no evidence of recurrent malignant disease. Gram's stain of the bile revealed numerous organisms, and a culture subsequently grew *Streptococcus* sp, *Escherichia coli, Klebsiella* sp, and clostridia. The operation proceeded uneventfully for two hours until, about ten minutes after the surgeons had manipulated the gallbladder, blood suddenly began oozing throughout the operative field. Spontaneous epistaxis also developed. The patient was hemodynamically stable at this time, with a mean arterial pressure of 75 mm of mercury, a heart rate of 58, and an oxygen saturation of 98%. Over the next ten minutes, bleeding became profuse and her mean arterial pressure began to fall. Fluid resuscitation with packed red blood cells, crystalloid, albumin, platelets, and fresh frozen plasma was begun. A central line was placed, but a peripheral arterial line could not be inserted. Arterial access was eventually accomplished by femoral cannulation. The patient's blood pressure continued to fall despite infusions of dopamine, norepinephrine, calcium, and epinephrine and the concomitant administration of crystalloid and blood. The bleeding could not be controlled. The operation was quickly completed. On arrival in the intensive care unit, the patient's systolic blood pressure was 40 mm of mercury, and she died three hours later despite continued attempts at resuscitation. She had received a total of 23 units of blood, 10 units of fresh frozen plasma, 16 units of platelets, and 14 liters of crystalloid. Intraoperative and postoperative study results are presented in Table 1.

TABLE 1.—*Hematologic and Coagulation Studies and Arterial Blood Gas Values Before, During, and After Surgical Procedure*

Laboratory Studies	*Pre-operative*	*Intra-operative**	*Post-operative†*
Hematocrit	0.387	0.266	0.21
Platelets, $\times 10^9$/liter	202	130	62
Leukocytes, $\times 10^9$/liter	5.3‡	...	...
Prothrombin time, sec (control, 11-13)	11.5	15.5	>100
Activated partial thromboplastin time, sec (control, 26-37)	26.9	72	>200
Fibrinogen, grams/liter§ (normal, 1.6-3.5)	...	1.8§	<0.02
Thrombin time, sec (control, 13-17)	...	22.5	>100
Fibrin split products (normal, <10)	...	>320	>320
pH	...	6.95	7.08
Po_2, mm of mercury	...	363	167
Pco_2, mm of mercury	...	33	50
Bicarbonate, mmol/liter	...	7.3	15.2
Fraction of inspired O_2	...	1.00	1.00

*Following the onset of uncontrollable bleeding.
†Measured in the intensive care unit.
‡The differential cell count was normal.
§Values given in Système International (SI) units; to convert to milligrams per deciliter, multiply by 100 (normal, 160 to 350 mg/dl).

Discussion

There are many factors that predispose patients who are candidates for surgical procedures toward the development of disseminated intravascular coagulation (Table 2), but severe DIC is rarely encountered.[3,5,6] Our case shows that fulminant disseminated intravascular coagulation may develop unexpectedly and raises questions as to the cause and the appropriate therapy for severe DIC.

The most remarkable aspects of this patient's course were the severity of the coagulopathy and the fact that it could not have been anticipated. Its severity is noteworthy in that severe DIC, although associated with a mortality of 86%, rarely results in bleeding serious enough to cause death.[5] In this case the coagulopathy worsened despite administering platelets, fresh frozen plasma, and blood. Bleeding was uncontrollable virtually from the moment it began. Although the patient had recognized risk factors for DIC such as a history of colon cancer and a recent intravenous pyelogram, she was not acutely ill nor did she have any clotting abnormalities preoperatively. Cholecystectomy is not thought to increase the risk for DIC. Nothing in this patient's history, physical examination, or laboratory results suggested that she was at risk for acute, severe intraoperative DIC. This case suggests that severe intraoperative DIC may occur unexpectedly in any patient who has risk factors for the disease.

We can only speculate as to the cause of acute disseminated intravascular coagulation in this patient. Unlike most patients with severe DIC, she was not critically ill, nor did she have organ system failure before it began. Recent abdominal operations have been implicated in severe DIC,[5] but in these patients it apparently follows the operation and occurs in conjunction with intra-abdominal sepsis. Severe DIC *during* an abdominal operation in the absence of massive

TABLE 2.—*Conditions Associated With Disseminated Intravascular Coagulation (DIC)*

Infections*	Sepsis (almost any bacteria, gram-positive or gram-negative); viral, occasionally fungal or protozoan
Malignant disease	Several types of solid tumors; leukemia, lymphoma
Obstetric	Preeclampsia, amniotic fluid embolus; retained fetus, abruptio placentae, abortion
Vascular surgical procedures	Aneurysm, cardiopulmonary bypass
Miscellaneous	Trauma, burns, surgical procedures (such as Levine shunt); hepatic disease, collagen disease; shock, and other causes

*In severe DIC, multiple infections are common.

trauma, sepsis, or vascular procedures has not been described. The link between DIC and malignancy is well established, but patients in whom severe DIC develops generally are acutely ill with their disease.[5,7] This patient had no evidence of active disease preoperatively or at laparotomy. Infections, often multiple, are the most common cause of severe DIC.[5] They are usually bacterial, but fungal, viral, and parasitic infections have been implicated. Preoperatively, this patient had no evidence of active infection. Her antibiotic therapy the day before her surgical procedure followed the generally accepted guidelines for patients undergoing bowel operations. She also received a cefalosporin the day of her operation, as is recommended for those patients who are thought to be at an increased risk for infection following cholecystectomy. This includes patients who have stones, jaundice, acute cholecystitis, or diabetes, or those older than 70 years.

Given the temporal relationship between the manipulation of the infected gallbladder and the onset of bleeding, it seems likely that despite appropriate preoperative antibiotic therapy, infection played a substantial role in the onset of DIC in our patient. The polymicrobial nature of the organisms cultured from the bile also may have contributed both to the development and the severity of the ensuing coagulopathy. Bile cultures with positive results are not unusual in this group of patients, however. In cases of chronic cholecystitis, 10% to 15% of patients are found to be colonized, as compared with 50% with acute resolving cholecystitis and 80% with florid acute cholecystitis.[9] The most common organisms found are *E coli, Klebsiella* sp, and *S faecalis,* but clostridia and *Bacteroides* and *Proteus* spp are also frequently identified.

Endotoxemia, although unproved, seems the most likely cause of the coagulopathy. Although endotoxemia is a well-established cause of disseminated intravascular coagulation, the mechanism by which it initiates DIC is unclear. Intrinsic system activation through endothelial damage caused by endotoxin is one possible explanation. This may occur through the modulation of tissue factor and thrombomodulin expression in the endothelium.[10] An endotoxin may exert its effect on the coagulation cascade by extrinsic system activation through complement activation, with subsequent activation of platelets and monocytes. At this time, the actual mechanism of endotoxin initiation of DIC remains speculative. Further support for the involvement of sepsis and endotoxemia would have been interesting in this case, but, unfortunately, blood specimens sent to the laboratory for culture were lost, and no limulus assay was done. We should emphasize that positive results on blood cultures would not have established endotoxemia or sepsis as the cause of DIC in this patient but would have increased our suspicion of their role in initiating DIC. Indeed, rarely does severe DIC occur in the presence of only one risk factor; multiple predisposing factors for DIC usually are present.[5,7]

Therapy in this patient focused on replacing coagulation factors. Heparin therapy was not attempted. This is consistent with the widely held belief—which, it should be noted, is not supported by adequate studies—that the most appropriate therapeutic approach to DIC is correcting underlying causes and replacing consumed factors.[7,8,11,12] Because heparin therapy has been advocated by some authors, we did consider its use.[11] The data on heparin use fail to consistently show any benefit, however. Because heparin therapy should at least in theory be of benefit, it has been suggested that heparin failure is caused by decreased antithrombin III levels during DIC.[13-15] Antithrombin III inhibits thrombin or activated factor X, and its action is accelerated by heparin. Studies using antithrombin III have thus far produced a variety of results. While no specific conclusions can be drawn, several investigators have reported impressive results using antithrombin III in disseminated intravascular coagulation, thus adding further controversy to the question of the role of heparin therapy in treating DIC. The question of the appropriateness of administering heparin to treat DIC is not yet resolved. Because its use is neither strongly supported nor condemned in the literature, clinicians must use their own judgment as to its appropriateness. In general, the lack of well-controlled studies addressing the treatment of DIC makes specific therapeutic recommendations impossible. The cornerstone of therapy remains correcting the underlying causes of DIC and possibly replacing consumed factors.[8]

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Circumcision

To the Editor: The American Academy of Pediatrics recently published a position paper that recommended against the routine circumcision of newborn males.[1] A similar view was expressed in this journal's Epitomes section.[2] When a correspondent[3] questioned these views, mentioning evidence that circumcised men have a lower incidence of sexually transmitted diseases, including AIDS, he and the editors were roundly criticized.[4]

In fact, three independent studies[5-7] provide evidence that human immunodeficiency virus I (HIV-I) infection is less common in circumcised men. Additional, unpublished data have been reviewed.[8] The most recent of these reports[5] notes that the risk ratio for HIV-I infection (uncircumcised: circumcised) may be as great as 8.2 (95% confidence interval, 3.0 to 23.0) and may actually exceed the risk incurred by frequent contact with prostitutes.

One must grant that these studies are recent; the authors of the position paper and the epitome may not have been able to take them into account. Nevertheless, the question of routine circumcision of newborns clearly remains open. Attempts to inhibit dissent from the opinions of "authorities" belong in the distant past. Otherwise, we would still be studying the teachings of Galen.

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The Canadian System

To the Editor: The editorial by Banks in the August issue implores us not to create a health care system that removes responsibility from patients to pay something for their care because, "Once a benefit is given . . . , it is politically impossible to take it away."[1] In fact, is that not exactly what the US Medicare program is doing? Previously promised benefits are being taken away from the elderly, and, further, where at first the benefits were free, now the patients are being forced to pay an ever-increasing share. So, it is politically possible for the Canadian government to renege, and it is only a matter of time until it does—in the interest of balancing its national debt. The politician's trick is to be sure that the blame for this falls on the providers (physicians).

Also, the glowing accounts of the Canadian system by Grumbach[2] and Burrow[3] ignore two facts that would prevent that system from working in the United States. First, in order for the Canadian system to work, it has extremely tight limits on the number of new doctors who may enter many regions of Canada. Can you imagine how long a US antitrust lawyer, hired by a recent medical school graduate, would let organized medicine get away with that in this country?

Second, the Canadians do not face the malpractice specter that we do in the United States. Their system would be much more expensive here than it is in Canada because of our huge malpractice premiums and the high cost of the defensive medicine that we all practice.

In short, it is the US legal climate that not only makes our system more expensive but will prevent a cost-effective national program from being developed in this country.

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Editor's Note:
Hear, hear!

MSMW

* * *

To the Editor: I read with interest the article on national health insurance by Dr Kevin Grumbach in the August 1989 issue.[1] A friend in the United States sent it to me and suggested that I reply. While it is no business of mine what the United States decides to do, the Canadian system was discussed in such laudatory terms I felt that it behooved me to present the toad's viewpoint.

> The toad beneath the harrow knows
> Exactly where each tooth-point goes;
> The butterfly [Grumbach] upon the road
> Preaches contentment to that toad ("Pagett, M.P.," Rudyard Kipling).

With socialism having demonstrably failed in eastern Europe, it never ceases to amaze me how young people like resident Grumbach still think that this is the preferred way to go. He finds the rag tag and bobtail of capitalism distasteful and wants to replace it with "meaningful health care planning," that is, centralized planning. The experts in centralized planning are the eastern Europeans, who have arguably the worst health care system in the civilized world. As cen-

tralized planning has never ever worked anywhere, why should it work in the United States? The typical socialist thinking is fairly obvious: "progressively financed" means the more you make, the more you pay (that is, "from each according to his ability, to each according to his needs"). If my recollection is correct, this was the doctrine of Karl Marx.

Dr Grumbach labors under the curious impression that if a central government runs anything, it will be more efficient than the private sector. I find it a little difficult to believe that in this day and age anyone other than a government bureaucrat would believe this old chestnut.

Dr Grumbach believes that the Canadian health system is the best available. He is hot against many things, including the capitation system of payment, which he thinks is the worst option. He obviously does not know that the Ontario government is pushing as hard as possible to introduce the capitation system into Canada.

Dr Grumbach lists the usual arguments against a national health service and proceeds to demolish them.

"It would cost too much." He states that Canada spends only 8.6% of its gross national product on health care. In Canada health care is run by the provinces or state governments. In Ontario the current government feels that health care costs are "out of control" and that between 25% and 35% of the total provincial budget is spent on health care, which is why they must cut back.

"It would impose a terrible government bureaucracy." Well, has it not?

"It would ration health care." It *does* ration health care. As a reasonably well known orthopaedic surgeon who specializes in joint replacement, my waiting list for this procedure is four years. I do not jest. As of this afternoon I am "booking joints" into May 1993. Last year my prosthetic budget was cut from almost $1 million a year to less than half a million. This means that I went from about 400 to 500 joint replacement procedures a year to 250. The bottleneck at the institution where I work is the cost of the implants. Hospitals are funded on a global budget. When budgets are cut or not increased, something has to be cut, and the most obvious thing is the implant budget. I get a printout every three months telling me how many joint replacements I can do. Unfortunately, emergency revision operations have emptied December's budget and, unless things calm down, November's also. This, of course, simply forces the patients to shuffle back up the line.

The state government has a statutory obligation to pay for implants but will not and will not let anyone else either—neither patient, nor company, nor insurance agency. If the patient comes from another country, he or she can pay for the implant, and it can, therefore, be done within a few days.

"It would prevent physicians from earning a respectable income." We do in Canada make a reasonable income but please do not trust government figures. When I was a boy I was told that there were lies, damned lies, and statistics. Nothing much has changed. The average physician's income is worked out after the incomes of the lowest 30% are discarded. Some average! Dr Grumbach thinks that we negotiate our fees with the state government. We did—before private practice was banned. As part of the agreement we were supposed to have binding arbitration. Unfortunately, the government did not like the arbitrators' recommendations and imposed a settlement. "He who pays the piper calls the tune," and a single payer can dictate. There is no recourse.

Dr Grumbach thinks that because the Canadian public likes the system, it is good. When I left the United Kingdom in 1971, it had a pretty poor health care system and yet the media and the public thought that it was the best in the world. Less than 10% of the population are exposed to health care problems, and how can the rest judge—from the media? The only people who know are those at the sharp edge. It is I—not some faceless bureaucrat—who has to tell the little old lady she has to wait four years for her hip replacement. The state government will provide money for a wheelchair but not the money for the hip implant to get her out of the wheelchair.

Canada is the only country outside of eastern Europe, and I have lectured in most of them, where a private contract between a patient and a physician is illegal. Does this produce a one-level egalitarian system? In a sense it does. The rich go to the United States for surgical procedures, and the rest wait unless they have some influence; in that case they "queue jump."

When I first came to Canada, the health care system, with its mixture of public and private options, functioned superbly. It has since been hijacked by the politicians and is on a rapid downhill course. This is recognized by all but those who make a Kennedyesque visit to Potemkin hospitals. As governments usually lack the will to repeal any socialist legislation, no matter how ill conceived, the situation will obviously have to deteriorate much further before "privatization" is reintroduced.

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Undergraduate Medical Education

To THE EDITOR: Your editorial on medical education in the August 1989 issue[1] touched on a variety of concerns these days for both practitioners and hospital medical educators. We tend to concentrate on issues with residency training and continuing medical education, which loom larger in the world of daily patient care, but we may overlook undergraduate medical education, the bedrock of our professional development.

Concerns about undergraduate education range from premedical preparation to medical school missions, preclinical versus clinical curricula, and residency counseling. Despite warnings and guidelines from a General Professional Education of the Physician (GPEP) report and from foundation think tanks, what happens in medical schools is still as hard to change as moving a cemetery. The process is further exam-locked by the National Board of Medical Examiners and others. Just try to defend a first year course on Clinical Evaluation of the Patient against the basic science faculty!

As was shown recently on the television show NOVA, changing the Harvard curriculum was heralded as a major breakthrough, even though light years behind other medical

schools. It was evident even in the film that the inability of faculty to adapt to better teaching techniques might well prove the self-fulfilling death wish of this innovation. Left to their own devices, specialty departments rebuild their walls and it's publish or perish for the academe.

One breath of fresh air in the 1970s was the legislative mandate for family practice training, a truly comprehensive approach to teaching, learning, and care. It was this discipline that enlisted more community practitioners to serve as role models, sponsored premedical experiences in local hospitals, encouraged increased communications skills, and provided psychologists for trainee group therapy. Nowadays, family practice has more and more of an uphill struggle to preserve itself among competing specialty departments.

With the current scene progressively influenced by third party payers, peer review, managed care, and high technology, opportunities abound for undergraduate medical education to thrive in new settings. Seed beds for the informed health consumer of tomorrow are the student health facilities of local colleges and universities. Nursing homes, clinics, and even house calls are returning as learning options. The resources are abundantly available; how soon will those responsible for undergraduate education take advantage of them?

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How I Kicked the Cigarette Habit

To THE EDITOR: In 1919 I entered the freshman class at the University of Nebraska Medical College. It was here that I first met a man whom I idolized from the start. I will call him Bill, since that was his name. He was a chain smoker. He was a good talker, and the way he could talk while blowing smoke from his mouth and nose and the way his cigarette dangled at a devilish angle from his fingers completely fascinated this green boy fresh from the farm. To me it was the ultimate in sophistication, and I wanted so much to look and act like him.

My first step, of course, was to light up a cigarette. At first I smoked OPs—other people's—but soon took to buying my own. I smoked one after breakfast, one after each class, one before and after lunch, one before and several after dinner. Then, I went home for Christmas, and during those two weeks, I did not smoke (Dad would have killed me had he known I smoked). But after New Year's I was back at it. Then came summer vacation and I had to go home again and help on the farm, so of course there was no smoking for three months.

Then I was back for the second year of school and back to smoking. One day, Bill was watching me smoke and suddenly said, "You're not smoking. You have to inhale to really be a smoker." "Show me what you mean," I said, and that was when I really became a smoker.

As the years went on, I continued to smoke more and more. I had no pep and nothing tasted good. I had pain in the pit of my stomach almost every day. It was about 1932 when I first decided to quit. I had severe withdrawal symptoms, but I started feeling better and had more pep and no pain. I stayed off cigarettes for six weeks, but then I was back on them. During the next 12 or 13 years, I must have quit 20 times but never for more than four or five days. I would go through withdrawal and then go back to smoking. I finally had to admit to myself that I simply could not quit. This was very depressing. Never before had I tried to do anything and completely failed. So, in about 1950 I took a vow never to try to quit again because all it got me was the withdrawal symptoms and failure.

And so the years rolled on. I had my habit, I had my yellow teeth, my yellow fingers, I had a house that constantly smelled of stale tobacco smoke, I had my stuffed up lungs, I had my fatigue, my irritability, and my depression. Most of all, I had that awful sense of failure.

And then came that day in 1953, a day that I shall never forget. I came home completely exhausted after a very difficult day, and my lungs were so stuffed up I scarcely could breathe. I asked myself what on earth was I going to do: "I can't quit but I can't go on like this. Maybe I should shoot myself." And suddenly I was thinking back to that first year of my smoking and how that summer was when I went home. I had quit smoking for three months and it was easy. Why? I know. I wasn't inhaling yet. So that's what I'll do. I won't quit, but I will stop inhaling. In that way I will stop damaging my lungs—and maybe my heart. And now comes the sequence of events that I am sure many of you will not believe, but I swear is true. Whenever I wanted to smoke, I lighted a cigarette. I made no attempt to cut down at all and entertained no thought of quitting. Almost at once the number I smoked dropped—after a week I went from 60 cigarettes a day to ten. After another week I was down to two cigarettes, and then I just quit. Most remarkably, I had absolutely no withdrawal symptoms. That was 35 years ago, and I have never, absolutely never, had a desire for a cigarette since then. In fact if someone else's smoke wafts my way, I get irritated and angry. People smoke in my company, and I am never tempted.

To anyone reading this, I recommend this method: keep on smoking but stop inhaling. In this way you will stop damaging your lungs and still keep the pleasure (if any).

You may wonder what happened to Bill. Well, he died over 20 years ago, I think of cancer of the lung.

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Death Certificates

To THE EDITOR: I am saddened but not too surprised at the omission of the mention of Dr Morhardt's classic book on death certificates[1] from Klatt and Noguchi's article, "Death Certification—Purposes, Procedures, and Pitfalls," in the September 1989 issue.[2] This appears to be another example of the chauvinistic attitude of allopathic medicine to osteopathic medicine.

In my several years of lecturing to medical students and interns, I found no knowledge of this excellent and comprehensive discussion of the logic behind the construction of a death certificate. It is obvious that this subject, which is so grossly neglected in medical schools and which is of such importance to families, actuaries, and public health authorities, needs to be reinforced to the instructors of our coming generation of physicians.

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* * *

Drs Klatt and Noguchi Respond

To THE EDITOR: We use only those references that can be personally reviewed by us. The reference cited by Dr Sarkin was not available to us. There are undoubtedly many other local publications on this subject available to physicians. We should like to stress, however, that one of the best reference sources for information on death certification is still the local registrar or recorder with whom these documents are filed. The registrar can assist physicians not only with proper terminology and wording but also with specific information regarding local statutes governing deaths that come under the jurisdiction of the medical examiner or coroner and with instructions for proper completion of demographic items.

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Warfarin and Stroke

To THE EDITOR: In his editorial on managing cardiac emboli,[1] Dr Burke mentions that it is "unclear" whether long-term warfarin therapy will reduce the incidence of strokes occuring in the context of atrial fibrillation. He goes on to say that it may be indicated "only in certain groups" such as patients with cardiomyopathy and "would not appear to be necessary" in persons younger than 60 years with lone atrial fibrillation.

These findings are not in accord with a well done, randomized, double-blind study comparing warfarin to aspirin or placebo. A statistically significant decrease in the incidence of stroke was shown after two years in patients on warfarin but not in those in the other groups. Some of these patients were as young as 41 years.[2]

Any review of atrial fibrillation and stroke should at least mention this study.

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* * *

Dr Burke Responds

To THE EDITOR: The trial referred to by Dr Bohr is the first placebo-controlled, randomized trial comparing the effects of warfarin and aspirin-placebo in the prevention of thromboembolic complications in chronic atrial fibrillation.[1] This article, published in January 1989, describes a landmark study. Unfortunately, publication deadline required my composition of my editorial before publication of this article.

This trial included 335 or 336 patients in each group. The results were impressive: 21 patients in each of the aspirin and placebo groups had embolic events compared with only 5 events in the warfarin group. Most of these five events occurred at "subtherapeutic" prothrombin levels or when the patients had to stop warfarin therapy. This study would appear to sway the preponderance of evidence in favor of warfarin treatment in patients with chronic atrial fibrillation.

Several limitations exist with the study by Petersen and co-workers that warrant further evaluation and investigation before we subject all patients with atrial fibrillation to long-term warfarin therapy. Although the Methods section states echocardiograms were done, the results of these are never mentioned in the Results or Discussion. Left atrial size is not discussed except in the Methods. Many causes for atrial fibrillation are not clearly defined. No mention is made of hypertrophic or dilated cardiomyopathies, two groups with high embolic rates when associated with atrial fibrillation. Although certain subgroups are listed, such as those with thyrotoxicosis and patients with a history of heart failure, the number of embolic events is never broken down into these individual groups in an attempt to define if only one subgroup would warrant the warfarin therapy. The end point of embolic events includes acute stroke. This was a clinical diagnosis in some cases because a "computed tomography (CT) scan was done when possible." The follow-up was limited to two years.

The warfarin treatment was not innocuous. A total of 21 patients had hemorrhage requiring drug withdrawal. Another patient had a fatal cerebral hemorrhage. Only two patients in the aspirin group and none in the placebo group had significant bleeding. Of the patients randomly selected for the warfarin treatment, 38% withdrew from the drug trial before the two years of follow-up.

Finally, this trial presents some results in conflict with previous studies. Unlike the large Framingham study with 30 years of follow-up,[2] this study did not show a correlation between age and the incidence of embolic events. The article by Petersen and colleagues does not state the mean period of follow-up. Assuming a maximal two-year follow-up on patients, the placebo and angina groups had an embolic event rate of 3.13 per 100 patient years. This is nearly six times the embolic rate of 0.55 noted in the large cohort of patients with lone atrial fibrillation that were followed by the Mayo Clinic.[3] Presumably the group of patients enrolled into the study of Petersen and co-workers included subgroups with a higher embolic risk than the subgroup of lone atrial fibrillation.

In conclusion, the publication this year of this randomized trial gives further impetus to provide anticoagulation therapy for our patients with chronic atrial fibrillation. Because of the concerns listed here, further evaluation of the results of this trial and further confirmatory trials are needed before we subject all patients with atrial fibrillation to long-term warfarin therapy.

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Occupational Medicine

Analysis of Pregnancy-Related Calls to an Occupational Hazard Hot Line

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Since 1980 the Hazard Evaluation System and Information Service has responded to over 11,000 inquiries regarding workplace health hazards. Of 2,424 inquiries in 1986, 593 (24%) concerned hazards to pregnancy. This represents a 17-fold increase since 1981. Most pregnancy-related inquiries were from employees (70%) and health care providers (23%). Referral sources for the employee calls were almost exclusively individual health care providers or institutions that provide health care or health counseling, or both. These data suggest that pregnant employees seek information on their own or from health care providers instead of from employers. Of the inquiries, 80% were for general pregnancy hazard information; 20% involved symptomatic pregnant employees. Most inquiries concerned employment in the services (58%) and manufacturing (26%) sectors. Organic solvents, pesticides, acrylic nail-grooming products, lead, and video display terminals were among the agents about which callers inquired most frequently.

(Wright C, Quint J: Analysis of pregnancy-related calls to an occupational hazard hot line. West J Med 1989 Dec; 151:670-675)

During the past decade, toxic substances in the home, community, and work environment have received increased attention. There is special concern about reproductive hazards in the workplace, where an estimated 50,000 chemicals are used and 3,000 new chemicals are introduced each year. Women are increasingly taking jobs that involve exposure to chemicals. Currently, women constitute close to 50% of the labor force in California, and a majority are of childbearing age.[1] Many women who are pregnant or planning pregnancy are now acutely aware of the chemical, physical, and biologic agents they encounter on the job.

One result of the growing awareness has been an increasing demand for information on workplace pregnancy hazards. Pregnant employees and others are thus turning to resources such as the Hazard Evaluation System and Information Service (HESIS) for information.

After the discovery of reproductive-system damage in male workers exposed to dibromochloropropane,[2] HESIS was established in 1979 by the California legislature to prevent such occupational illnesses. The Hazard Evaluation System and Information Service is mandated to maintain a repository of current toxicologic and occupational health literature and to provide up-to-date information on the health hazards of workplace materials. In addition to its other functions described elsewhere,[3] HESIS provides information through its hot line, the Telephone Inquiry/Response System (TIRS), to employees, employers, health care providers, unions, and government agencies within California.[4] Since 1980, this hot line has responded to more than 11,000 inquiries, including over 2,000 regarding the effect of occupational exposures on pregnancy. Risk to pregnancy is now the primary interest of over 30% of callers.

Other pregnancy information systems have been developed in California and elsewhere, but they tend to focus more on drug usage and low-level chemical exposures in nonoccupational settings.[5-8] Our eight-year experience operating the TIRS hot line has enabled us to present descriptive data on concerns about reproductive hazards in the workplace and to comment on some issues we have encountered.

Methods

After confidentiality has been assured, information in the following categories is obtained from callers and recorded on a standard form:

- Primary interest (including—in order of highest to lowest priority—risks to pregnancy, relation of symptoms to work, or general health hazard information)
- Referral source
- Substances
- Exposure
- Question
- Caller (employees, employers—including supervisors, managers, company health and safety and medical personnel—health care providers, governmental representatives, and others).

Information—callers, substances, primary interests, questions—is recorded in a logbook, and callers and primary interest categories are coded prospectively.

Data were summarized for three time periods: 1981 through 1986, 1983, and 1986. The number of pregnancy-related inquiries and callers' occupations and organizations were counted from the logbooks for the period 1981 through 1986. Data on referral sources were obtained by consulting original inquiry forms from 1983 and 1986. Industries, occupations, and agents of concern, agents most frequently

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CTR = California Teratogen Registry
HESIS = Hazard Evaluation System and Information Service
SIC = Standard Industrial Classification
TIRS = Telephone Inquiry/Response System
VDT = video display terminal

inquired about, symptoms, and staff recommendations were obtained by consulting original inquiry forms for 1986.

Results

Figure 1 shows the annual volume of pregnancy-related TIRS inquiries and the total inquiry count from 1981 through 1986. The number of inquiries concerning risks to pregnancy increased dramatically during this six-year period. There was a 17-fold increase between 1981, when 34 pregnancy-related inquiries were received, and 1986, when the number totaled 593. The proportion of all pregnancy-related TIRS inquiries increased from 4% in 1981 to 24% in 1986.

In addition to information concerning pregnancy risks, for which an average of 217 inquiries per year were received, callers also requested general health-hazard information on workplace agents (average of 848 inquiries per year) and asked about the work-relatedness of symptoms (average of 303 inquiries per year). The overall increase in calls in 1985 and 1986 was because of an increased number of requests in all three categories. Requests for general health-hazard information showed the greatest volume increase.

New callers usually reach the TIRS through referrals by organizations or by persons familiar with it. The amount of advertising of the TIRS has been limited and did not change substantially between 1981 and 1986. To determine whether the increased volume of pregnancy-related inquiries had been generated by new referral sources, we compared the referral patterns for 1983 and 1986. These data are shown in Table 1.

The Toxics Information Center, a hot line primarily for nonoccupational exposures and hazardous materials emergencies, was the only new source of referrals since 1983 but generated only 33 additional calls in 1986; hence, new referral sources did not account for the overall increase in pregnancy-related inquiries. Instead, the increase was because of more referrals from all existing sources. The California Teratogen Registry (CTR), which provides risk counseling primarily for prescription drug use,[8] referred only six callers in 1983 compared with 200 in 1986 and currently represents our largest source of referrals. Health care providers are generally familiar with the CTR and are likely to call it themselves or to refer patients to it when questions arise regarding reproductive effects of workplace agents. In turn, CTR counselors refer to the TIRS callers concerned about occupational exposures. Table 1 also shows that most referrals are from individual health care providers and institutions or agencies providing health care or health counseling or both. Consistent with this fact, most (83%) repeat callers were genetics counselors, physicians, and nurses.

Figure 2 shows the frequency of pregnancy-risk inquiries by major caller group from 1981 through 1986. Most requests were from employees and health care providers. Before 1984, the number of calls from employees and health providers was about the same. Beginning in 1984, however, a much higher proportion of calls was received from employees.

Table 2 shows the caller distribution for 1986 pregnancy inquiries. Employees accounted for 70% of the inquiries; 23% were from health care providers including physicians (57%), genetic counselors (26%), and nurses (17%). Most physicians who called were in private practice (72%); fewer were associated with hospitals or clinics (23%).

Only 3% of the 1986 pregnancy-related calls were from employers, and only 1% were from government agencies. The government agency calls were from the California Occupational Safety and Health Administration medical and industrial hygiene personnel and from state and county health department personnel.

As shown in Figure 3, which summarizes 1986 data, calls

TABLE 1.—*Referral Sources for Pregnancy-Related TIRS Inquiries, 1983 and 1986*

Source	1983 No.	1983 (%)	1986 No.	1986 (%)
Previous callers*	15	(26)	43	(7)
Government agencies†	8	(14)	35	(6)
California Teratogen Registry	6	(10)	200	(34)
Hospitals and clinics‡	3	(5)	79	(13)
Physicians	8	(14)	57	(9)
Literature and conferences	3	(5)	33	(6)
Poison control centers	2	(3)	28	(5)
Toxics Information Center	..	(..)	33	(6)
Miscellaneous other	4	(7)	38	(6)
Unknown	9	(15)	47	(8)
Total	58	(99)	593	(100)

TIRS = Telephone Inquiry/Response System

*Repeat callers; no referral.
†Primarily the California Occupational Safety and Health Administration.
‡Primarily Kaiser Foundation Hospitals, California, in 1986.

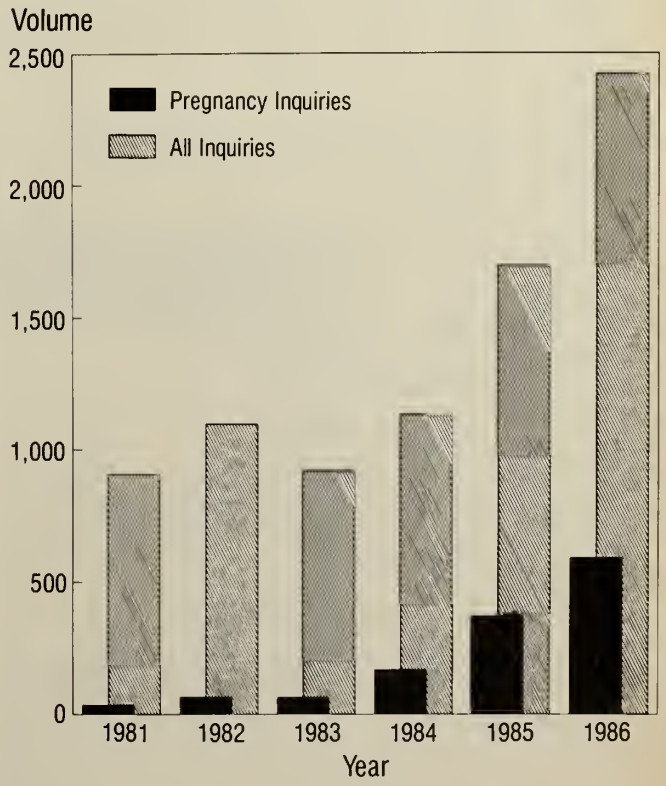

Figure 1.—The annual volume of all inquiries to an occupational hazard hot line is compared with that concerning pregnancy.

TABLE 2.—*Caller Distribution for Pregnancy Inquiries, 1986*

Caller	No.	(%)
Employee	416	(70)
Health care provider	136	(23)
Employer	19	(3)
Government agencies*	6	(1)
Other†	16	(3)
Total	593	(100)

*California Occupational Safety and Health Administration accounted for 4 of 6 government agency calls.
†Includes unions, insurance companies, attorneys, and the like.

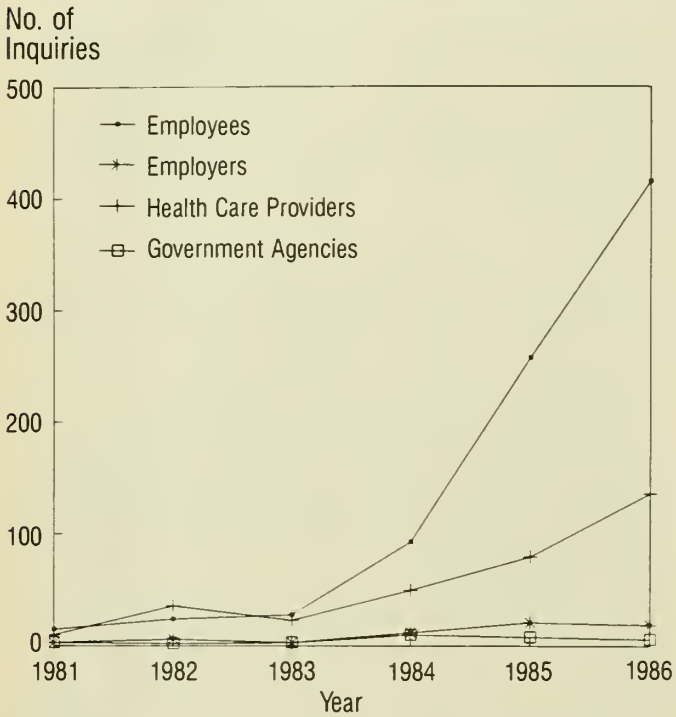

Figure 2.—The annual frequency of pregnancy-related inquiries to an occupational hazard hot line by caller group is shown.

were received regarding pregnant workers in all sectors of California industry. Most inquiries concerned employment in service (58%) and manufacturing (26%) industries. As a point of reference, the service and manufacturing sectors represented 29% and 14%, respectively, of all nonagricultural employment of women in California in 1986.[10] Tables 3 and 4 describe typical occupations and agents of concern in the service and manufacturing industry inquiries.

Approximately 40% of service sector inquiries concerned employment in the business services (Standard Industrial Classification [SIC] code 73) (Table 3). Most (65%) of these employees were office workers. Their primary concerns included the use of video display terminals (VDTs) and exposure to organic solvents in carpet adhesives and paints, pesticides, and roofing tar fumes. Since chemical exposure of office workers generally is transient and involves low airborne concentrations,[11-14] it usually presents little hazard to pregnancy. Radiation levels of VDTs, perceived to be a pregnancy risk by many office workers consulting the TIRS, have not been found excessive when measured.[15] While a recent study did suggest that some women using video display terminals for more than 20 hours a week were at increased risk for spontaneous abortion, no definite association was made between abortion and VDT use.[16]

Table 4 shows that jobs in the electronics industries (SIC code 36) were the primary occupations of concern in the manufacturing sector. Typical agents inquired about were organic solvents, including methylene chloride and ethylene glycol monoethyl ether (an animal teratogen), a variety of acids, and two human reproductive toxicants—lead and ionizing radiation.

The agents most frequently of concern with regard to pregnancy risks are listed in Table 5. Almost half the agents are organic solvents, which probably reflects their widespread use in California workplaces. We generally recommend that pregnant employees minimize their exposure to organic solvents because these lipophilic substances are usually capable of reaching a fetus. Most organic solvents, how-

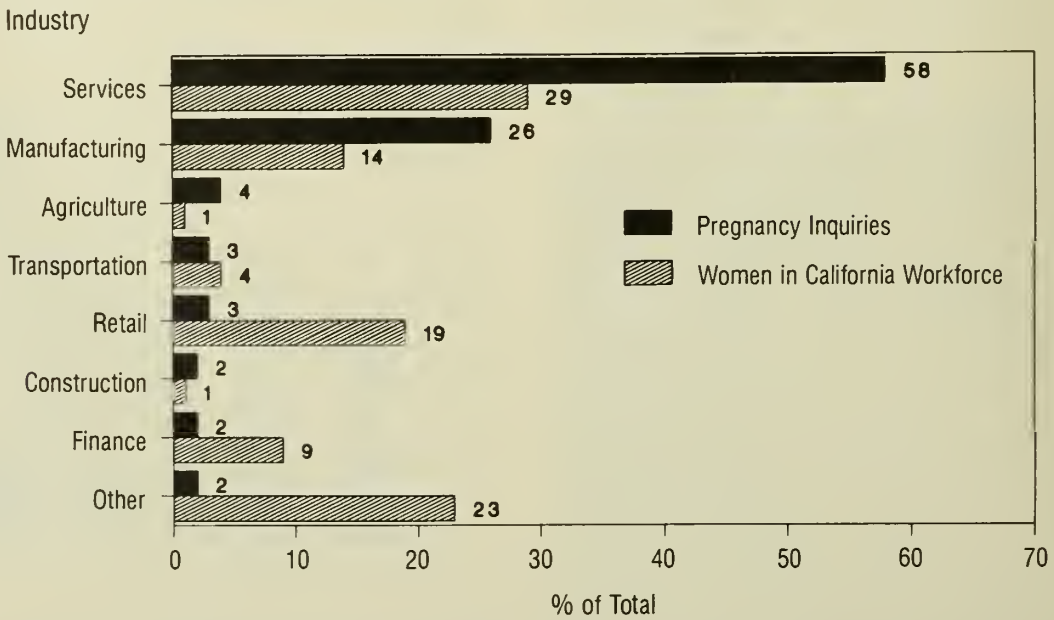

Figure 3.—The 1986 distribution (%) by industry of inquiries to an occupational hazard hot line is compared to the percentage of women in the California workforce working in that industry.

ever, have not been adequately studied, and their potential effects on a fetus remain unknown. Frequent inquiries about common acids and ammonia show the need to increase employees' understanding and awareness of hazards as part of hazard communication training, if only to alleviate inappropriate concern, since these agents are not expected to cause adverse effects on reproduction.

Of the 593 pregnancy-related inquiries received in 1986, 80% were simply requests for information about workplace hazards to pregnancy. Concern about symptoms in pregnant employees was expressed in 20%, or 119, calls. Of these calls, 84% were made by the pregnant employee, while 13% were made by a health care provider calling on behalf of a patient.

Inquiries about symptom-related pregnancy primarily were from employees in the services (45%) and manufacturing (29%) sectors. Most frequently reported symptoms were consistent with central nervous system (CNS) depression and eye, nose, and throat irritation. Only a few calls concerned spontaneous abortion, stillbirth, or birth defects.

After careful evaluation of the information provided by the callers, responses to the symptom inquiries included the following:

- General toxicity and industrial hygiene information

TABLE 3.—*Service Industries, Typical Occupations, and Agents Inquired About During Pregnancy-Related Inquiries, 1986**

Industry†	*Occupation*	*No.*	*Agents*
Business (N=115‡)	Office workers	75	VDTs, carpet adhesives, pesticides, roofing tar fumes, paint
	Photo lab technicians	16	Hydroquinone, acetic acid, aluminum thiosulfate, silver nitrate, organic solvents, mercuric chloride
	Blueprint operators	6	Ammonia
Health (N=62)	Dental assistants	15	Nitrous oxide, mercury, radiation, methyl methacrylate
	Nurses	8	Antineoplastic drugs, formaldehyde, ethylene oxide
	Hospital workers	7	Ethylene oxide, glutaraldehyde, antineoplastic drugs
	Hospital lab technicians	6	Xylene, miscellaneous organic solvents, formaldehyde
	Laboratory technicians	6	Ethidium bromide, biologic hazards
Personal (N=57)	Manicurists	26	Acrylic nail-grooming products (acrylates)
	Cosmetologists	18	Hair dyes, permanent-wave solutions
	Custodians	6	Ammonia, alcohol, sodium hypochlorite (bleach), cleaners containing glycol ethers
Miscellaneous (N=29)	Artists	15	Organic solvents, epoxy resins, fiberglass, pigments, lead
	Writers	4	VDTs, organic solvents
Engineering, accounting, research, management, and related services (N=19)	Lab researchers	8	Formamide, benzene, hydrazine, chloroform, mercury
Educational services (N=15)	Teachers	11	Pesticides, organic solvents, carpet glues, methanol, roofing tar fumes

VDT=video display terminal

*Represents employee industries based on inquiries from employees, employee representatives, and employers. Total service industry inquiries=314.
†*Standard Industrial Classification Manual*, 1987.
‡N=Total inquiries per industry.

TABLE 4.—*Manufacturing Industries, Typical Occupations, and Agents Inquired About During Pregnancy-Related Inquiries, 1986**

Industry†	*Occupation*	*No.*	*Agents*
Electronics and electrical machinery and supplies (N=51‡)	Electronics assemblers, solderers, wafer fabricators, microchip handwashers and inspectors	45	Lead, solder flux, ethylene glycol monoethyl ether, other organic solvents, acids, phenol, radiation
Printing, publishing, and allied industries (N=24)	Printers	10	Organic solvents, inks, acrylic monomers, polyglycols
	Print-shop workers	3	Trichloroethane, isopropanol, ethylene glycol monobutyl ether
	Bookbinders	2	Organic solvents
	Photolithographers	2	Hexamethyldisilane, xylene
Fabricated metal products, except machinery and computer equipment (N=9)	Electroplaters	3	Nickel, cyanide, nitric and sulfuric acid, sodium hydroxide
	Solderer, degreaser, packer, fabricator	4	Ethylene glycol, xylene, Freon, acetone, hydrogen fluoride
Chemicals and allied products (N=7)	Chemical workers	2	Methylene chloride, phosgene
	Herbicide manufacturing workers	2	Hexachlorobenzene, hexachloropyridine, monoethanolamine
Food and kindred products (N=7)	Tortilla maker	1	Graphite, kerosene
	Fumigator	1	Ethylene oxide, methyl bromide
	Winery worker	1	Sulfur dioxide
	Cannery worker	1	Chlorine dioxide
Transportation equipment (N=5)	Aerospace parts etcher, window maker, parts cleaner, assembler	4	Toluene, xylene, methyl ethyl ketone, nitric acid, acetone, hydrochloric acid

*Represents employee industries based on inquiries from employees, employee representatives, and employers. Total manufacturing industry inquiries=142.
†*Standard Industrial Classification Manual*, 1987.
‡N=Total inquiries per industry.

when exposure appeared to present no increased risk to the pregnant worker (40%). For example, a pregnant office worker exposed to irritating ammonia vapors from a blueprint machine was informed about the toxicity of ammonia and was reassured that the exposure would not pose a risk to the fetus;

- Specific advice on reducing exposure when there was a possibility of increased risk from overexposure (29%). For example, a pregnant anesthesiologist experiencing headaches at work was advised of the risks associated with exposure to anesthetic gases and of the need to reduce her exposure to them. We recommended that the scavenging system be inspected, repaired, and air monitoring done;
- Recommendations that pregnant workers be removed from exposure when the likelihood of an increased risk of an adverse outcome was high (13%). For example, an electronic wafer fabricator using many organic solvents and suffering CNS depression was strongly urged to stop her current work, preferably through a job reassignment or disability leave if available.

Included in the remaining responses were advice to file a complaint with the California Occupational Safety and Health Administration and recommendations for medical surveillance or specific laboratory tests. Information on disability leave and employees' legal rights was also provided for persons advised to reduce exposure to—or avoid altogether—potentially dangerous agents.

Discussion

An increased use of the TIRS to obtain information about workplace pregnancy hazards and the proliferation of other pregnancy hot lines in the past decade reflect the public's growing concern. The variety of industries, occupations, and workplace agents represented in our data base indicates that concern about workplace hazards to pregnancy is felt by women in all sectors of California's work force.

Employees and health care providers were the major groups requesting pregnancy risk information through the TIRS from 1981 through 1986. In contrast, employers, government agency representatives, and union representatives—who called frequently for information on general health hazards of workplace agents and the work-relatedness of symptoms—rarely called about pregnancy hazards.

Referral sources for pregnancy-related inquiries were almost exclusively health care providers or institutions that provide health care or health counseling or both. Again, this contrasts with the referral pattern for non-pregnancy-related inquiries, for which the California Occupational Safety and Health Administration was a major referral source.

The referral pattern and caller distribution of pregnancy-related inquiries suggest that women initially seek information on their own or from their health care providers instead of from their employers. Because of a fear of discrimination, pregnant employees may not consult employers; if employers are consulted, they may in turn refer employees to their health care providers.

Employers may not provide relevant advice and training about pregnancy risks because this information is often not included on material safety data sheets, which appear to be employers' primary source of health hazard information. Several factors contribute to this lack of information. First, reproductive toxicity data are rarely available because most agents have not been tested for this end point. Second, even when data are available, it is often difficult and sometimes impossible to extrapolate outcomes in animal models to outcomes in humans. Agencies analogous to the National Toxicology Program, which routinely conducts standardized animal cancer tests on chemicals, and the International Agency for Research on Cancer, which evaluates the results of cancer bioassays and cancer epidemiologic studies, do not yet exist as resources for obtaining information on potential reproductive toxicants.

The limitations we have described make it difficult to assess the risk to pregnancy from workplace agents. Employers, however, still have the initial responsibility to provide training, because this is legally mandated by the Hazard Communication Standard. In addition, employers have access to information regarding the extent of employees' exposure to workplace agents that is essential for assessing potential health hazards. That so few employers call for information and that so few women are referred by their employers suggest that this mandated training is not being conducted.

Health care providers should not be expected to assume an employer's role as the primary source of information about workplace pregnancy hazards. Our calls indicate that most health care providers lack a knowledge of workplace agent toxicity to reproduction and rarely know the extent of employees' exposure to potentially harmful agents. Health care providers do, however, have a responsibility to their

TABLE 5.—*Agents Most Frequently of Concern in Pregnancy-Related Inquiries, 1986*

Agent	*No. of Inquiries**
Organic solvents, not otherwise specified	45
Pesticides	41
Acrylates†	39
Acids	34
Paints	33
Acetone	30
Ammonia	24
Lead‡	23
Video display terminals	23
Xylene§	23
Isopropanol	21
Fluorocarbons	19
Trichloroethane§	19
Toluene§	17
Formaldehyde	14
Methyl alcohol§	14
Methylene chloride§	14
Nitrous oxide‖	14
Petroleum distillates	14
Solder fumes	13
Glycol ethers‖	12
Methyl ethyl ketone§	12
Photography chemicals	12
Mercury, metallic‖	11
Permanent-wave products	11
Hair dyes	10

*Number of times agent was inquired about may not represent distinct consultations since one consultation often involved multiple agents.
†Acrylic nail products (N=34); methyl methacrylate (N=5).
‡Known human reproductive toxicant.
§Possible human reproductive toxicant.
‖Probable human reproductive toxicant.

pregnant patients to consider workplace risks. They should routinely obtain an occupational history and ask about workplace exposures. This is best done before pregnancy or during early prenatal visits. Combining information about workplace exposure to toxic agents with nonworkplace factors such as nutrition, genetic risk factors, smoking history, and alcohol and other drug intake is important when weighing risks for adverse pregnancy outcomes. Training in occupational health and reproductive toxicology is essential for ensuring that risk assessment is done adequately.

In assessing risks to their pregnant patients, health care providers must often distinguish between "worried-well" employees, such as office workers transiently exposed to low concentrations of organic solvents in carpet adhesives, and "potentially-at-risk" employees, such as electronics workers regularly exposed to high concentrations of organic solvents and experiencing symptoms consistent with overexposure. Several information sources can assist health care providers in making this distinction.[17-19]

Health care providers should also be aware of and prepared to respond to certain medicolegal issues that we have encountered with increasing frequency. A key issue is whether pregnant women should continue working during pregnancy. This decision must be made on a case-by-case basis and should take into account each woman's desire or need to continue working and the potential for reproductive harm if she does so. Unfortunately, only limited options are available to pregnant employees who decide to stop working.[20] An important recourse involves qualifying for pregnancy-related disability, as employees who are disabled because of pregnancy legally must be treated the same as any other disabled employee; however, the scope of a pregnancy-related disability has not been defined. Regardless of an employer's disability policy, current California law allows pregnant women four months of unpaid leave.

A new and growing controversy now affecting health care providers concerns "letters of certification," an apparent attempt by some employers to avoid potential liability. These letters are sent by employers to pregnant employees' health care providers. Often accompanied by an extensive list of chemicals, the letters ask health care providers to review the list and certify that no harm will come to the employee or her fetus from continued chemical exposure. Some women have been threatened with layoff if the letter is not returned with a physician's signature. It is impossible for anyone to guarantee freedom from risk, and health care providers should not feel responsible for doing so. Coercing physicians to sign such letters or laying off employees whose physicians refuse to sign raises legal issues yet to be addressed. We advise health care providers not to sign letters of certification. If, as a result, pregnant patients are threatened with job loss or another form of discrimination, they should be referred to an agency or organization representing employees' legal rights.

Conclusion

Until there is routine testing and identification of potential reproductive toxicants, guidelines for assessing their risks, occupational health standards reflecting reproductive toxicity, and improved implementing of the Hazard Communication Standard, complex medical, legal, and toxicologic issues will continue to arise. Meanwhile, pregnant employees should not be made responsible for obtaining reproductive toxicity information. Employers are obligated to provide a safe work environment and accurate information on toxicity of agents and exposures to them in the workplace, and health care providers are responsible for guiding pregnant women in making appropriate, informed decisions regarding potential health risks.

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Evolving Residency Requirements for Ambulatory Care Training for Five Medical Specialties, 1961 to 1989

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Recent changes in the patient population of teaching hospitals, spurred by technologic advances and economic forces, have jeopardized the traditional hospital-based model of residency training. In consequence, there has been increasing attention paid to the need for ambulatory care experience. A primary force in shaping the content of postgraduate medical education is "The Essentials of Accredited Residencies," published in the Directory of Graduate Medical Education Programs. *We reviewed recommendations and requirements for ambulatory settings and outpatient experience as specified in the* Directory *during the years 1961 to 1988 and investigated pending changes in requirements for five major specialties: internal medicine, pediatrics, family practice, general surgery, and obstetrics and gynecology. Increases in the amount of time residents spend in ambulatory care training recently have been mandated in internal medicine and are under consideration in two other specialties, indicating probable major shifts in the locus of postgraduate medical training.*

(Zones JS, Schroeder SA: Evolving residency requirements for ambulatory care training for five medical specialties, 1961 to 1989. West J Med 1989 Dec; 151:676-678)

Graduate medical education traditionally has consisted almost exclusively of intensive experience in an inpatient setting.[1] Changes in the pace and content of hospital care, driven by economic and technologic forces, have called into question the educational validity of a hospital serving as the dominant training site for most specialties.[1-3] These changes, which have been discussed elsewhere,[4] include the greater severity of illness among patients in hospital, decreasing lengths of stay, a growing concentration of patients in intensive care units, a shift in patient management decisions out of the hospital, and the increasing importance of specific procedures as a reason for admission to hospital. These developments have generated a great deal of discussion within academic circles about the need for and possible obstacles to shifting some graduate medical education from hospital to ambulatory settings.[5] In response to these events, the Council on Graduate Medical Education recently recommended increased residency training in ambulatory sites.[6]

A driving force in shaping the curriculum and training experiences of residency programs is the Accreditation Council on Graduate Medical Education (ACGME), which, through the institutional residency review committees for each medical specialty, stipulates requirements for approved residencies and accredits residency programs accordingly.[7,8] Programs that fail to meet the requirements risk a loss of accreditation. Changes in the requirements of the various residency review committees would provide strong incentives to shift more training to ambulatory settings. We reviewed recommendations for ambulatory care education by the ACGME for the period 1961 to 1989 for five major specialties (internal medicine, pediatrics, family practice, general surgery, and obstetrics and gynecology) to assess whether their requirements have changed in response to the perceived need for more training in ambulatory care.

Methods

The sections on "Essentials of Approved Residencies" of the 1961 through 1988 editions of the *Directory of Graduate Medical Education Programs* (commonly referred to as the "green book") were reviewed for the five specialties. Each suggestion, recommendation, or requirement regarding the use of ambulatory settings for clinical training, outpatient experience, and length of residency was noted. In addition, we spoke with staff of the ACGME who are official contacts for the individual specialty residency review committees to learn about impending changes not yet incorporated into the green book.

Results

Over the past three decades, there has been a general lengthening in residency training, although internal medicine and family medicine have been three-year programs throughout the period of study (family medicine was first approved as a specialty in 1969). The length of residencies in pediatrics was two years in 1961 but increased to three years in 1978. General surgery stipulated four years of training from 1961 until 1979, when a five-year minimum was initiated "in most instances." In 1983 a five-year requirement

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TABLE 1.—*Evolving Residency Requirements for Ambulatory Care Training for 5 Specialties, 1961-1989*

Specialty	*Year*	*Specified Recommendations and Requirements*
Internal Medicine	1961	No mention is made of ambulatory care
	1971	Training should include experience in social, ambulatory, preventive, and rehabilitative aspects of medicine; no specifics mentioned
	1980	Residents should spend at least 1 half-day per week in ambulatory care
	1989	Ambulatory experience in each year of training, with at least 25% of the 3 years in an ambulatory care setting; continuity care in at least 2 and preferably 3 years
Pediatrics	1961	Clinical training should be obtained in outpatient clinics
	1978	There must be an equivalent of at least 6 months in ambulatory pediatrics during the 3 years; at least a portion of ambulatory experience consisting of continuing care is recommended
	1980	There should be weekly or biweekly assignment to a continuity clinic for at least 2 years
	1985	Continuity requirement increased to 3 years; patient populations specified to include children with variety of chronic diseases
Family Practice*	1969	Residents should be responsible for comprehensive and continuing care to a select group of patients
	1979	Residents to have opportunity to provide continuing care for a specified panel of patients over at least 2 years
	1983	Assignment to family practice center specified as at least 1 half-day per week during the 1st year of residency, 2 to 4 half-days the 2nd year, and 3 to 5 half-days during the 3rd year
General Surgery	1961	Valuable experience may be obtained from outpatient services
	1979	Adequate outpatient service considered necessary
	1983	Active participation in outpatient services is essential
Obstetrics and Gynecology	1961	Outpatient facility is essential
	1982	Ambulatory training is essential, with a ratio of outpatient visits to admissions documenting this emphasis

*Family practice was created as a specialty in 1969.

was instituted for all programs in general surgery. Obstetrics and gynecology residencies were three-year programs in 1961 but required four years for those beginning graduate medical education after 1976. Changes in ambulatory training for the five specialties are shown in Table 1.

Internal Medicine

Before 1971 no mention was made of ambulatory care for internal medicine residencies. At that time, the subject was alluded to in recommending ambulatory as well as social, preventive, and rehabilitative experience as part of training. No specified amount of time for ambulatory training was mentioned for internal medicine until 1980. At that time, the green book required that the "continuity experience should be at least a half day per week." Whether this expectation pertained to all three years is not clear. Although most internal medicine residency training programs now provide ambulatory experience throughout the three years of training, there are many that do not. In September 1988, the ACGME approved changes in the wording of the "essentials" of residency programs in internal medicine that would clarify this requirement and its importance in determining accreditation. As of October 1989, internal medicine residencies must include ambulatory care experience in each of the three years of residency training, with at least 25% of the three years in an ambulatory care setting, including emergency departments. Continuity care must occur in at least two of the years and preferably three.

Pediatrics

Requirements for ambulatory training in pediatrics residency programs increased steadily over the past decade. In 1961 programs were to provide clinical training in outpatient clinics. In 1978 a six-months' minimum experience in ambulatory training was instituted, with the recommendation that at least a portion of that consist of continuing care. In 1980 it was added that there should be a weekly or biweekly assignment to a continuity clinic for at least two years. The recommendation was made a requirement for the entire three years of residency in 1985, with the stipulation that the population served include children with a variety of chronic illnesses. Contemplated changes call for ambulatory experience beyond that now required in the continuity clinics, particularly with acutely ill patients and with adolescents.

Family Practice

Family practice is a specialty based on ambulatory care, with a fundamental requirement by the Family Practice Residency Review Committee that clinical education take place in a model ambulatory practice. Thus, it is not surprising that from the outset (1969) it was specified that residents be responsible for comprehensive and continuing care to a select group of patients. In 1979 the language was refined to refer to care for a specified panel of patients over at least two years. By 1983 the green book recommended increasing amounts of time to be spent in designated family practice centers, from one half-day per week during the first year of training, to between two and four half-days during the second year, and from three to five half-days during the third year.

General Surgery

For most of the time period studied, the essentials of general surgery suggested that outpatient and follow-up services could be "valuable." In 1979 the provision of an adequate outpatient clinic or service to see patients before admission to and following their discharge from hospital was specified. By 1983 active participation in outpatient services was made an essential component of graduate education in general surgery, and experience in office practice was deemed desirable. Nevertheless, the type and duration of ambulatory experience is not defined. The general surgery representative at the ACGME reports that this specialty's residency review committee has been working on substantial changes in requirements for some time. Current proposals would require experience with patients before surgical admission and at follow-up after release from the hospital and would specify what constitutes acceptable evidence of this experience—including notes on patients' charts.

Obstetrics and Gynecology

As shown in the table, ambulatory care requirements for obstetrics and gynecology are similar to general surgery, though with somewhat greater emphasis. Between 1961 and 1982 the availability of an ambulatory care facility was noted as being "essential" to residency program approval. In 1982 ambulatory training was described as essential, and ratios of outpatient visits to admissions were to provide evidence of emphasis on ambulatory care for accreditation review. No particular ratio was suggested. As with general surgery, no expectations regarding the type of experience or amount of time are detailed for ambulatory care rotations.

Discussion

A review of changes in the requirements for ambulatory care training, as defined by the various residency review committees and their parent organizations, indicates that increasing importance is being given to ambulatory care experience in preparing future physicians. There is considerable variation across the specialties examined. Internal medicine, family practice, and pediatrics are the most explicit in requiring that residency training be conducted in ambulatory settings. These three specialties also call for a substantial portion of time devoted to ambulatory training throughout the three years of residency. Changes in the requirements for ambulatory training in internal medicine residency programs approved in 1988 by the ACGME require 25% of a resident's time be devoted to ambulatory care throughout the residency period. This planned shift follows a decade of increasing emphasis on ambulatory care. The changes in internal medicine requirements are all the more remarkable in light of the fact that as recently as 1984, one program was threatened with loss of accreditation because its general internal medicine program featured spending at least 25% of time in continuity care, that being considered too great a proportion of residency experience by the review committee (S. Wartman: "The RRC and the '25 Percent Rule,' *SREP-CIM Newsletter,* 1985; 7:2-3). General surgery and obstetrics and gynecology also seem to be giving greater emphasis to ambulatory training, although without specific guidelines for program directors.

Although accreditation guidelines for each of the specialty programs examined address ambulatory care education, they do so with more or less specificity with regard to requirements. Family practice, pediatrics, and internal medicine address the amount of time to be spent in outpatient care. To the extent that requirements in "The Essentials of Approved Residencies" are a force in shaping the content and process of graduate medical education, revisions in these requirements provide a clear signal about the importance that the leaders of clinical education give to ambulatory care.

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Commentary

Alternative Health Care

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One summer evening in my youth back in a small midwestern town I watched a street-corner spellbinder show us how his particular brand of "snake oil" would penetrate and disappear when applied to a slab of shoe leather.

"Ladies and gentlemen, step right up. Let me show you how this magic potion, when rubbed on the skin, will cure migraine headaches, bilious attacks, female disorders, eggzema and pimples. Get 'em while they last, folks, 35¢ a bottle, two for half a buck."

He was a convincing pitchman, and business was brisk. At that time in my life, 35¢ took a large chunk out of what I made on my paper route, but this itinerant healer seemed honest; he was charming; and that lotion surely disappeared through the shoe leather, just as he said it would . . . and, I had pimples. I handed over my three dimes and a nickel.

This almost forgotten vignette came back to me when I read an editorial in *The Western Journal of Medicine* titled "Integrity in Medicine."[1] In that essay Dr Watts cited "dishonesty, plagiarism, and outright fabrication of results at some of the most prestigious research institutions in the nation." He pointed to incidents of fraudulent activities by medical students and dishonesty in billing third parties by practicing physicians.

What is happening to our proud profession? Are we by default undermining the public's faith in us, spurring the growth of alternative health care?

By coincidence, at about that same time I was invited to sit in on a public forum at a Spokane television station. The subject under discussion was to be "Alternative Health Care Practices."

Attending this program was an enlightening experience for me. Among the 60 or 70 members of the audience were perhaps a half dozen physicians representing what was referred to as "traditional medicine." The rest were practitioners of various "alternative" callings and their "clients." The implied assumption was, of course, that there is a crying need for an alternative to the traditional type of health care.

Sitting to the left of me was a midwife, behind me an acupuncturist, in front was a homeopathic "specialist," and to the right of me, a "reflexologist." You might say I was well surrounded.

As planned, the program was dominated by the alternative health care providers. The "reflexologist" was given time to explain how, after attending several seminars put on by The International Institute of Reflexology in Florida, he was able to treat all areas of the body by applying acupressure on specific "zones" of the feet.

The naturopaths, the homeopaths, and the acupuncturists all followed, telling the television audience of their many therapeutic successes. They brought along their happy, satisfied clients to give glowing testimonials.

Under the white heat of the television lights, the outnumbered physicians tried to make calm and rational statements about the scientific practice of medicine, the need for adequate professional training, the requirements for double-blind crossover studies to prove the efficacy of medicines or treatment modalities, and the desirability of protecting patients through the certification of health care practitioners. This was like chaff thrown into the wind. For example, when an oncologist told of his concerns about the tragedies that have occurred when alternative care givers treated patients with serious organic illnesses—diabetes, heart disease, cancer—these were quickly passed over as nonexistent worries.

The recurring themes expressed by this audience, often with great emotion, were that there are a lot of bad apples out there in traditional medicine; physicians are just specialists who pass out deadly pills, rather than treating the whole patient; and they just treat the symptoms rather than "the person."

The alternative practitioners stated repeatedly that they and they alone could relieve stress and tension by changing the flow of life forces, improving the circulation, and by flushing out body toxins, thereby restoring the humoral balance.

The carefully worded responses of the physicians seemed futile, compared to the colorful comments coming from the rest of the group. We were uncomfortably on the defensive. I came away from this program convinced that we "traditional" physicians are not doing a good job of polishing our public image. I had to ask myself, are we really looked upon only as pill peddlers and button pushers? Have specialization and technology distanced us from our patients?

Within our ranks we scoff at copper bracelets and the "zones" and the "meridians" of acupressure and acupuncture. Embracing our ever-enlarging array of magnificent pharmaceuticals, we ridicule the use of Chinese herbs or the tiny doses of homeopathic medicines. Could it be, perchance, that we are missing the boat? Do we need to open our eyes to the progressive evolutionary changes taking place in the health care delivery system? How well I remember the shame I felt as a pre-med student when one of my cousins confided he was going to follow the "short course" into medical practice by taking the osteopathic pathway. At that time in my mind osteopathy was on the fringe of quackery. How that has changed. By gradually bringing their educational and training programs up to the standards of allopathic medicine, the DO now ranks alongside the traditional MD.

(Fox ERW: Alternative health care. West J Med 1989 Dec; 151:679-680)

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Chiropractic is struggling to sharpen its image. Indeed, modern chiropractic is a far cry from the teachings of David Daniel Palmer when in 1895 he set up his Palmer College of Chiropractic. In those early days the chiropractic course could be completed in a few short months. Now it requires four years and includes basic sciences, physical therapy, and the anatomy and physiology of the musculoskeletal systems.

It is apparent that physicians are becoming more tolerant of chiropractic treatment as long as the practitioners stick to those tasks—backache, injuries, the bone and joint problems—that they are trained to treat. We can conjecture that there are other subtle forces—licensing restrictions, Medicare requirements, professional liability—that have caused these practitioners to stay within the limits of their accepted capabilities. With respectability comes responsibility.

There were several convictions I carried away from the public forum. The first was that as we observe the ascending degree of the alternative practitioners' training, those at the lowest level are the loudest in their condemnation of traditional medicine and the most emotional and outspoken in describing the cures they could achieve. Conversely, as we moved upward, away from witchcraft and cultism, the practitioners are more rational in their statements and less critical of legitimate medical practice.

Finally, I was reminded that I could learn a few things about patient care from these alternative practitioners: little skills of listening, of projecting warmth and compassion, and of touching and the laying on of hands. Moreover, if I disparage the work of the alternative care givers, am I at the same time losing sight of the fact that, as Dr Watts commented in another editorial, there is a "lessening of the confidence of society as a whole in physicians and the medical profession"? And that "It is still the patient who seeks help and the physician who uses the art and science of the profession to give the help that is needed."[2]

In our devotion to the science and the technology of medicine, are we guilty of forsaking the art? I may deride "faith healing" until I remember that I use it every day in my practice. Years ago I spent my precious 35¢ on snake oil because I had faith in the words of the vendor. My pimples healed.

There lived 2,000 years ago a highly respected alternative practitioner who said to His patient, "Arise, take up thy bed and walk."

And His patient walked.

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Lessons From the Practice

Summary Judgment

ELLIOTT B. OPPENHEIM, MD, *Bellevue, Washington*

Ah, docta, ah see you haav cheeldrun." Her Mississippi drawl was unmistakable as she referred to the crayon drawing my seven-year-old, Laura, had done.

I looked at the septuagenarian with crinkled skin who greeted me with a broad smile as I entered the examination room. It was the middle of flu season. I thought if I had to look at another glowing eardrum or beefy sore pharynx, I'd scream. For a moment this woman seemed like an oasis—a resting spot to recharge my batteries.

"Yuah lookin' at me funna, docta. Awl ah want is t'haav yuah wash out mah eahs. Ham gettin a hearin' ahd next'h week 'n theya got some wax in theya."

She wiggled a bony arthritic finger into her right "eah" to better illustrate what was needed. She was obviously up "heah" visiting someone for the holidays. The reason I looked at her funny, and I admit I did, was that she had a growth like a black potato chip on the right side of her nose; it looked like a basal cell or squamous cell cancer, for sure.

I looked at her funny again, and she said, "Theyat's from mya glasses. Damn thing won't heal. Ah haad t'bout six months oah moah."

She created a rehearsed, theatrical smile; it was stiff, almost as if cued from a director, so I was not surprised when she told me something else. "Ah was once in vaudeville. Ah knew awl the greats . . . singin', dancing', awl'v thaat . . . I'm a Christian Scientist."

The last bit, the Christian Scientist revelation, caught me off guard. "My ex-wife's aunt was a Christian Scientist . . . ," I told her to enlist some common feelings. What I didn't tell her was that Aunt Cecelia died a horrible death in a frothing bout of congestive heart failure. I remembered seeing her drown in her own secretions and being annoyed when I knew she could have lived another ten years with a couple of bucks of digitalis and diuretics.

"Don't . . . touch . . . me," Cecelia managed in between wet gasps. "I'm Christian Science. God's my doctor." I recalled Aunt Cecelia's last words as I extended my finger to touch the blackish growth. Mrs Adams parried my well-intentioned finger with a quick brush of her hand.

"Don't . . . Ahm Christian Science . . ." she reminded me and smiled. "Don't sayah 'nother wuhd . . ."

I knew enough to back off, wash out her ears, and let her go. I felt I had to respect her age, her conviction, her religion . . . but . . . but.

While her daughter waited for her in the reception area, I took advantage of the time it would take for Mrs Adams to dress. By Aesclepius, Hammurabi, and Hippocrates, by the souls of Semmelweis, Osler, and Cushing, by the sacred trust of all physicians, I had an obligation to at least bring the disfiguring reality to discussion. She would have those cancer cells in her brain soon. Why, with only a few dollars' worth of plastic surgery and several rads of radiation . . . More intimately than any other human beings, physicians know and understand the secrets of life and death. I knew what would happen to her.

I couldn't ignore this. If untouched, the cancer would eat her face away as if torn by a hungry crab. I'd seen the ravages of basal and squamous cell carcinomas in South American indians who have no treatment.

In a hushed and cautious voice I spoke to her grateful daughter. Both of us sensed that this was a clandestine discussion forbidden by the patient's desire but mandatory by all that is good and decent in physicians caring for patients and daughters caring for mothers.

When my patient appeared in the reception room, she saw us and in a controlled but furious voice stated, "You betrayed me, docta, you betrayed me."

"I have an obligation . . . ," I sputtered.

"You betrayed me."

I was both disappointed and angry, frustrated by the obvious paradox of this impotent confrontation with serious disease. I knew she had every right to die whatever way she wanted.

She could just tap dance herself right out of my office. Fine with me if she didn't want my medicine. Yet in my mind's eye, in my doctor's heart where I pray that nothing bad happens to my patients, I saw this aged vaudeville dancer in a different way.

I remembered a man in Quito with one third of his face gnawed away by just such a cancer. The globe of the eye was exposed and rotated around like a hideous cyclops in order to see. Although it would be wrong to interfere with this woman, it would be *more* wrong to say nothing.

As the office door clicked behind them, I turned and saw a logger who was waiting to have a cut stitched. I felt embarrassed. He'd overheard it all, I surmised. He wore heavy boots and a plaid shirt, and any director would cast him as Paul Bunyan. He looked up at me and seemed to know my despair. "Doc, ya did the right thing. Don't matter what she said. Ya did the right thing."

(Oppenheim EB: Summary judgment. West J Med 1989 Dec; 151:681)

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Lessons From the Practice

Show and Tell

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Kim conceived in the spring. She began her prenatal visits for this, her second pregnancy, in the early summer. All was normal as we began to know each other, for she had delivered elsewhere when her son, Joshua, now seven and a first grader, was born.

Joshua always accompanied his mother and took great interest in her enlarging tummy. And when we first heard the fetal heart with the dopptone stethoscope, he was beside himself with joy. He also was a willing subject for the dopptone and took to pulling up his shirt and saying, "me, me," at the end of each examination.

The summer progressed, as did the pregnancy. Fall came and Joshua started school, but Kim arranged her visits so he could continue to come along. And then one day as we were all in the examining room listening to the baby, Joshua piped up, "Can we all go to school for show and tell?"

His mother and I looked at each other. I said, "It's all right with me." She said, "It's all right with me, but we'll have to ask your teacher."

It was indeed all right with the teacher, and arrangements were made. Kim and I met in the hall of the school at the appointed time and were ushered into the classroom.

Joshua proudly introduced us. And as 30 bright, shining faces hung on my every word and watched my every movement, I explained that Joshua's mom had a baby inside and we were going to listen to it. Kim lay down on the table and we all listened to the baby's heart. Then I asked if any of the children would like to hear their hearts. Joshua was first, followed by about ten others from the class.

The questions were all about the baby. How big is it? Can it see? Can it hear? When will it be born? (Despite my fears, they did *not* ask the obvious question, although their teacher and I had discussed what our response would be in that event.)

But as I fielded these questions, I began to sense what it is that motivates teachers. Having these 30 young faces watching my every move and having these children hang on my every word was an exhilarating experience.

Kim finished her pregnancy and had a healthy boy.

I'm certain Joshua and his classmates will remember our show and tell for a long time.

I shall never forget it.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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(Bratman RL: Show and tell. West J Med 1989 Dec; 151:682)

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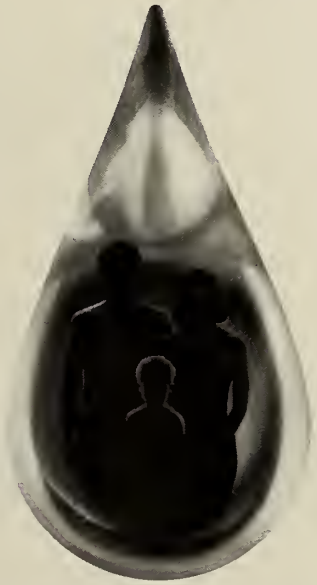

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CLASSIFIED ADVERTISEMENTS
THE WESTERN JOURNAL OF MEDICINE
P.O. BOX 7602, SAN FRANCISCO, CA 94120-7602
(415) 541-0900, ext. 376

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

BC/BE FAMILY PRACTICE opportunity in Tucumcari, New Mexico. Must be willing to do OB. Financial assistance with income guarantee. For more information, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy three physician Family Practice group (including OB) seeks replacement for partner departing fall 1989. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three to five weeks paid vacation; seven paid holidays; malpractice, medical, dental, and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry, Carol Sweig or Jim Ellis, Directors, northern California, (415) 673-7676 or (800) 437-7676. In southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

BC/BE FAMILY PRACTITIONER sought to join an established practice in the community of Artesia, New Mexico. Income guarantee available for the right individual. Family oriented community with year round recreation and fully equipped 38-bed hospital. Please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

CALIFORNIA—NORTHERN. Area's leading private practice group has immediate and future positions for BC/BE Family Practice and Primary Care Physicians in its Department of Ambulatory Care and General Medicine. Excellent compensation, incentive program, full benefits, early equity position, retirement plan. Experience lifestyle and professional fulfillment in beautiful northern California. Call Maureen Forrester: (408) 282-7833. Send CV to San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112.

NORTH CENTRAL IDAHO

17 physician multispecialty group recruiting BC/BE partners.

- 2nd Dermatologist
- 2nd Gastroenterologist
- 3rd General Internist
- 6th Pediatrician

Progressive medical community. Outstanding recreational area. Excellent life-style.
Send CV to:

Bob Baker, Administrator
Valley Medical Center and Children's Clinic
2318 Vineyard Ave
Lewiston, ID 83501
(208) 746-1383

PHYSICIANS WANTED

Join the leader and enjoy your practice!

Family Practice

Pacific Physician Services
A dynamic and growing 65-physician Southern California medical group network, has immediate career opportunities for primary care physicians. Examine our benefits:

- $8K monthly guarantee;
- Monthly FFS productivity incentives;
- Paid malpractice;
- Medical & dental plans;
- Retirement, disability;
- Vacation, CME, sick time.

Discover an enjoyable practice, call

Ruthan Smith
(800) 338-4798
or (714) 825-4401 in CA

INTERNAL MEDICINE, NORTHERN CALIFORNIA. You have a unique opportunity to join the area's leading multispecialty private medical practice. A position is available immediately for a BE/BC Internist. All subspecialties welcome to apply. Generous salary, bonus provision, fringe benefit package, and early membership in the corporation. Accept the challenge; become part of our competitive, growing organization. Experience the good life—wonderful restaurants, beautiful scenery, great weather, cultural facilities, easy access to beaches and mountains. Send CV and receive further information by contacting Christy Jensen or Maureen Forrester, Physician Recruitment, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833, (408) 282-7757.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CALIFORNIA. BC/BE HEMATOLOGIST/ONCOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

CALIFORNIA. BC/BE OTOLARYNGOLOGIST to join 14 MD multispecialty group with progressive practice environment located in a small city in the central San Joaquin Valley at the foothills of the Sierras, two hours from the coast. Send CV to Kaweah Medical Group, Attn: Maya Ricci, 222 W. Willow, Visalia, CA 93291.

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PHYSICIANS WANTED

NEUROLOGIST

BC/BE, full- or part-time, for expanding San Francisco bay area private practice with emphasis on clinical Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
240 Polk St
Box 337
San Francisco, CA 94109

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; telephone 1 (800) 544-1987.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist or Family Practitioner at 260-bed community hospital in the rapidly growing South of Market area. Excellent opportunity to build or join busy practices. Competitive salary and benefits package. Send CV to Walter Kopp, St Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BC/BE FAMILY PRACTITIONER sought for small community on the western slopes of the Rocky Mountains. Income guarantee available for the right individual. For more information on this opportunity, please send CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

BC/BE FAMILY PRACTICE opportunity in the resort community of Ruidoso, New Mexico. Financial assistance with income guarantee. Beautiful mountain setting with easy access to all forms of recreation. For further details, please send your résumé to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext 8300.

PHYSICIAN OPPORTUNITIES IN ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 90 plus physicians in Tucson, Green Valley, and Tempe, Arizona, has positions available in these cities in Internal Medicine, Pediatrics, OB/GYN, Orthopedics, General Surgery, Urgent Care, and Family Practice. Excellent fringe benefits and profit sharing program. Fee-for-service, as well as owned HMO. Must be BE/BC. Call or write James J. Vitali, CEO, Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; (602) 322-8300.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIANS WANTED

INTERNAL MEDICINE. Long established multispecialty group in central Washington needs Internist. Independent contract or join partnership later. University town with many cultural and recreational activities. Send CV to Medical Building Associates, 200 E. 6th, Ellensburg, WA 98926, or call (509) 925-9891.

MD TO ASSIST in busy Orthopedic clinic and Operating Room. Will also take call. Position has been used in the past as a bridge to orthopedic residency. Attractive salary and excellent benefit package. Washington State licensure required. Available immediately. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200-12th Ave S., Seattle, WA 98144; (206) 326-4111.

GENERAL PRACTICE—SOUTHEAST WASHINGTON. 32 physician multispecialty clinic needs full-time physician as second physician in Immediate Care Center. Center is part of main clinic and has full range of ancillary and consultative services available. Abundant free time with no on-call responsibility. Excellent school system. Outstanding recreational and cultural opportunities. Guaranteed salary with excellent fringe benefits. Contact Robert Caudill, MD, or David Maloney, Administrator, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; (509) 525-3720.

SAN FRANCISCO BAY AREA. BE/BC Internist. We currently are seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 prepaid Health Plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to Michael Getzell, MD, Chief, Dept of Internal Medicine, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545.

PHYSICIANS WANTED

PROGRESSIVE MULTISPECIALTY GROUP

of over 20 physicians, located in Tracy, one of the most rapidly growing cities in northern California. Located in the San Joaquin Valley with diversified economy and excellent schools. We are looking for the following:

DERMATOLOGY
OTOLARYNGOLOGY
OB/GYN
NEUROLOGY
ORTHOPEDICS
PEDIATRICS
PODIATRY

Applicants must be BC/BE. Offering an excellent salary with an incentive arrangement and a competitive benefit package, leading to partnership after 18 months.

Reply with CV and references to:

Physician Recruitment
Eaton Medical Group
445 W. Eaton Ave
Tracy, CA 95376

GYNECOLOGIST needed for 78-bed JCAHO hospital. We are growing and we need to enlarge our specialty staff. Just opened new Cancer Treatment Center. 12,000 community, 90,000 immediate service area, 160,000 catchment area. Great outdoors area, cattle, oil, gas, hunting, fishing, good schools, low crime, ideal area for raising children. Reasonable malpractice rates. Send CV to Marilyn Bryan, Community Hospital, PO Box 2339, Elk City, OK 73648; (405) 225-2511.

WASHINGTON STATE
ROCKWOOD CLINIC, PS

An expanding 65 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY	HEMATOLOGY/ONCOLOGY
CARDIOLOGY	OB/GYN
DERMATOLOGY	RHEUMATOLOGY
INTERNAL MEDICINE	GENERAL SURGERY

FAMILY PRACTICE—permanent, part-time, locum tenens

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

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PHYSICIANS WANTED

CALIFORNIA, ARIZONA OR UTAH YOUR CHOICE

There are private practice opportunities now available in the following Humana California, Arizona and Utah communities:

LOS ANGELES COUNTY, CA

OB/GYNs— A two-physician group located next to our hospital in the western San Fernando Valley is now seeking an associate. Busy solo OB/GYN also seeks associate.

PHOENIX

CARDIOLOGIST—Regionally respected 20 physician Cardiology group here is now seeking to add another Cardiologist.

FAMILY PHYSICIANS—Option to join a group of two, a solo FP who seeks an associate, or purchase two well-established practices.

LAYTON, UTAH

FAMILY PHYSICIANS—Associate needed to join young, board-certified Family Physician in newly opened office. Layton is 12 miles south of Ogden and 15 miles north of Salt Lake City.

For further information, send your CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-12, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®

RADIOLOGIST. Part-time position available immediately in small hospital with general radiography and fluoroscopy, mammography and ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join progressive six physician group in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Dr Larry Casalino, 225 S. Cabrillo Hwy, Half Moon Bay, CA 94019.

PUGET SOUND. BC/BE Family Practitioner for new branch office of multispecialty clinic. Full Family Practice opportunity, OB optional. Guaranteed starting salary and benefits. Respond with CV to Memorial Clinic, Attention: Inge Hart, Personnel, 500 N. Lilly Rd, Olympia, WA 98506; (206) 456-1122, ext 249.

UROLOGIST, southern California. Urology group seeking new highly qualified BC partner. Ability in all radical surgery, ESWL, Endourology, prostheses, etc desired. Excellent smog-free coastal locale. Busy, expandable practice. Send CV to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ONCOLOGIST NEEDED for multispecialty group practice in Seattle; affiliated with University of Washington. Full-time clinical with potential for research. Diverse patient population includes managed care, fee-for-service, retired and active duty military. Attractive salary plus incentive and excellent benefit package. Send CV or contact Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

PHYSICIANS WANTED

KAISER PERMANENTE®

Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

GENERAL SURGEON BC/BE sought to join busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC SURGEON BC/BE sought to join two physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MEDICAL ONCOLOGIST BC/BE to join expanding 32 physician multispecialty group practice located in the foothills of the Blue Mountains in the state of Washington. The clinic serves a population area of 150,000. Full range of Radiation Oncology services are available in the community. Excellent schools, cultural and recreational opportunities. One junior college and two four-year colleges are located in the community. Guaranteed income with excellent benefit program. Send CV to Connie Goude, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

HAWAII. Family Practitioner needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

ENDOCRINOLOGIST NEEDED to join a busy solo Endocrinologist in a growing southern California city. Established referral base, 300-bed acute care hospital. Competitive salary leading to partnership. Reply with CV to Number 169, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGY. Cardiologist BC/BE to join two other Cardiologists in eight physician multispecialty clinic in Seattle. Extensive invasive/non-invasive opportunities. Send CV to PO Box 364, Seahurst, WA 98062.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Specialists and Primary Care Physicians—CIGNA Healthplans invites you to join our innovative and dynamic managed health care team. Our multidisciplinary HMO practice provides a supportive and collegial work environment at 31 locations. You will enjoy a wealth of cultural and recreational activities, access to major academic centers, and an excellent compensation package. *Call collect* **(818) 500-6570** *or send CV to* **Robert Harrington, MD, Professional Recruitment, CIGNA Healthplans of California, 505 N. Brand Blvd, Ste 400-49, Glendale, CA 91203.**

PEDIATRICIAN BC/BE sought to join four physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OBSTETRICIAN/GYNECOLOGIST BC/BE sought to join three physician department in busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MARICOPA COMMUNITY MEDICINE ASSOCIATES of Phoenix, Arizona, is staffing 60 plus physicians, physician assistants, and nurse practitioners for Maricopa County's ambulatory care clinics at various locations in the Phoenix metropolitan area. General Practice, Family Practice, and Internal Medicine specialist openings. Maricopa Medical Center, Dept of Community Medicine, 4th Floor, 2601 E. Roosevelt, Phoenix, AZ 85008; (602) 267-5288.

TUCSON, ARIZONA. BC/BE, residency trained Family Physician sought to join busy solo Family Physician in private practice. Attractive start-up package available. Send CV to Herb Jalowsky, MD, 1701 W. St Mary's Rd, Tucson, AZ 85745; (602) 622-1414.

NORTHERN CALIFORNIA. Rapidly expanding HMO in the San Francisco bay area is currently seeking three highly motivated BE/BC Family Practice/Emergency Room Physicians for the Urgent Care Center in a career and/or temporary position. Our 228-bed community hospital offers excellent specialty support, flexible hours, and competitive salaries. Career physicians are offered many benefits including malpractice insurance, medical, dental, and group life insurance, vacation, sick and educational leave, excellent retirement benefits, and special arrangements for physicians transferring from established practice. For more information, please send CV or contact Edward Cheng, MD, Dept of Urgent Care, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119-1197; (408) 972-6110. EOE.

ENDOCRINOLOGIST. Outstanding opportunity for a BC/BE Endocrinologist to join busy hospital-based group in Berkeley. Send CV to Randall Ammon, MD, Endocrinology Dept, 3001 Colby St, Berkeley, CA 94705.

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PHYSICIANS WANTED

CALIFORNIA AND WESTERN STATES

Opportunities for BE/BC physicians in metropolitan and rural areas in ENT, Internal Medicine, Family, General Surgery, Nephrology, Neurosurgery, OB/GYN, Orthopedics, Pediatrics, Urgent Care, others. **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

DIAGNOSTIC RADIOLOGIST to join five member group covering two small hospitals in northern California. Call (916) 877-8092.

UNIVERSITY PHYSICIANS. Student Health Service, University of Wyoming, Laramie, is seeking physicians for full-time employment. Applicants must have a Medical Doctor's degree plus be BC/BE by either AAFP or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the state of Wyoming. Prefer candidate to have at least four years of primary care experience. Physicians to join two full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. Closing date: October 25, 1989, or until positions are filled. Send inquiries and/or CV to Albert H. Roth, MD, Acting Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, Wyoming 82071. EOE/AA.

CALIFORNIA MULTISPECIALTY. Cardiologist, Anesthesiologist, Infectious Disease Specialist, Internal Medicine, Pediatrician, Endocrinologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist, Pathologist, General/Thoracic Surgeon. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center, 17821 S. Pioneer Blvd, Artesia, CA 90701.

FAMILY PRACTICE. The Kaiser Permanente Medical Group's northern California facility in Napa is seeking a BC/BE Family Practitioner to fulfill general clinic and hospital duties. Members of our large, multispecialty group earn highly competitive compensation and outstanding benefits including malpractice insurance, medical, dental, and group life insurance, vacation, educational leave, an excellent retirement program, and special arrangements for physicians transferring from established practice. For more information, please send CV to B. Parmeter, MD, The Permanente Medical Group, 3284 Jefferson St, Napa, CA 94558. EOE.

NORTHERN CALIFORNIA—San Francisco bay area. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large prepaid HMO offering competitive salary, job security, shareholder status, and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Dept, Kaiser Permanente Medical Center, 1200 El Camino Real, South San Francisco, CA 94080-3299, or call (415) 742-2516. EOE.

ACADEMIC INTERNIST—Los Angeles area—general or subspecialty. Primarily inpatient teaching—Family Practice residents. Full-time. Director, Northridge Hospital Family Practice Residency, 18406 Roscoe Blvd, Northridge, CA 91325.

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NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting physicians in a variety of specialties for positions throughout our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

MARTINEZ

Emergency Physicians — Join friendly, relaxed and highly professional colleagues at our 204-bed hospital in the heart of the San Francisco Bay Area. We are seeking experienced physicians, BE/BC preferred. Locum Tenens and part-time work available Summer/Fall, 1989 & Winter/Spring, 1990. Recent adjustments provide excellent hourly rate plus paid malpractice. Career positions also available, providing salary and excellent benefits package. Send CV to: Ted Bayer, M.D., Chief, or Andrea Wagner, M.D., Asst. Chief, Department of Emergency Services, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1000, ext. 3316 or (415) 372-1124.

Internists and Cardiologist (BC/BE) - Join us in our high quality, expanding, 25 member Department of Medicine where you will benefit from our university affiliated internal medicine residency program. Faculty appointment available. This East Bay suburban setting has excellent schools, and is only 25 miles from San Francisco. Please send CV, or contact Michael Melewicz, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 200 Muir Road, Martinez, CA 94553. (415) 372-1069.

ROSEVILLE

General Internists (BC/BE) — Immediate openings for California licensed Internists at our Roseville facility, 90 miles from San Francisco or Sierra skiing & camping. University associated residency program. Send CV to: Tony Cantelmi, M.D., The Permanente Medical Group, Inc., 1001 Riverside Blvd., Roseville, CA 95678.

SAN JOSE

Family Practitioner (BC/BE) — Our 228-bed Santa Teresa Medical Center serves 128,000 members. Predominately outpatient practice located in Silicon Valley, approximately 45 minutes south of San Francisco and 30 minutes from the Pacific Coast. Send CV to D. Bardole, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119.

Surgeons (BC/BE) - One General Surgeon and one Surgeon to do both general and vascular surgery. We are a 9 surgeon department with modern offices adjacent to the 228-bed hospital equipped with 7 operating rooms. We handle a full range of general, thoracic, vascular and plastic surgery cases, and our group includes about 100 fully trained physicians in all specialties. Please apply to the Oakland address below.

SOUTH SAN FRANCISCO

Seeking highly-motivated **BC/BE Internists and a BC/BE Gastroenterologist-Internist** for this expanding practice adjacent to our 125-bed community hospital. Send CV to: Mark Cole, M.D., Dept. of Medicine, The Permanente Medical Group, Inc., 1200 El Camino Real, So. San Francisco, CA 94080.

FAIRFIELD

Excellent opportunity for **BC/BE Family Practitioner** to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Forward CV to: Steven Freedman, M.D., The Permanente Medical Group, Inc., 1550 Gateway Blvd., Fairfield, CA 94533. (707) 427-4260.

Members of our large, multispecialty group earn a highly competitive salary and excellent benefits including scheduled time off, malpractice insurance, medical, dental and life insurance, and a substantial retirement program. Our physicians are free to concentrate on providing quality health care, without the burdens of managing a practice.

To inquire about other openings with our successful, growing medical group, send CV to: Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-5114, The Permanente Medical Group, Inc., 1814 Franklin, 4th Floor, Oakland, CA 94612. (415) 987-4949. EOE

KAISER PERMANENTE

Good People. Good Medicine.

(Continued from Page 699)

PHYSICIANS WANTED

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND

is again expanding and has positions available in the following areas for locum tenens or permanent employment:

Allergy
Anesthesiology
Emergency Medicine
Family Practice
General and Vascular Surgery
OB/GYN
Oncology
Orthopaedic Surgery
Otolaryngology
Psychiatry
Pulmonology
Urology

To inquire, write:

Director of Medical Staff Personnel
Group Health Cooperative of Puget Sound
521 Wall St
Seattle, WA 98121

PHOENIX, ARIZONA. Maricopa County, Department of Corrections is seeking Internists, General and Family Practitioners, and Certified Physician Assistants. Prefer experience in adult ambulatory care. Five weeks paid vacation, ten holidays, one week CME. Excellent hours—minimal on call. Paid malpractice. Paid health insurance. Facilities include both infirmary and family practice clinic settings providing a good working atmosphere. Send CV to Maricopa Medical Center, Dept of Community Medicine, 2601 E. Roosevelt, Phoenix, AZ 85008; (602) 267-5288.

ONCOLOGY/HEMATOLOGY. Excellent opportunity for Hematologist/Oncologist to join busy Hematology/Oncology practice in central California. Work as little or as much as you want. Excellent salary and opportunity for partnership. Reply to Number 174, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CENTRAL CALIFORNIA (FAMILY PRACTICE). We have an opening for a Family Practice Physician. Clinic is a 17,000 square foot primary care facility located near Bakersfield offering medical, dental, lab, x-ray, and pharmacy services. Excellent salary and benefit package. Call George Johnston, (805) 845-3731, for details or write PO Box 457, Lamont, CA 93241.

HEALTH OFFICER

Fresno County Department of Health has an excellent opening for Health Officer/Medical Director. Responsibilities include medical consultation, liaison with medical community, media presentations, medical peer review, communicable diseases. Contract arrangement with salary and time commitment negotiable. Fresno offers outstanding lifestyles, recreation, and housing values. Please send CV to **George Bleth, Director of Health, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3200.**

CALIFORNIA, NORTHERN. A stable group of four ABEM certified/eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rogue, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1000, San Francisco, CA 94104.

SAN FRANCISCO BAY AREA. Contemporary General Internist with academic interest sought to join thriving, prestigious private practice on Oakland Pill Hill. Reply to Number 179, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO NORTH BAY AREA/NAPA VALLEY. Immediate openings (career and part-time) in a multidiscipline Emergency Department for physicians trained in Emergency Medicine, Internal Medicine, Family Practice, or Pediatrics. Full in-house multispecialty coverage. Complete generous benefit package. Contact Robert Mack, MD, Kaiser Hospital, 975 Sereno Dr, Vallejo, CA 94589; (707) 648-6200. EOE.

PULMONOLOGIST BC/BE (INTERNAL MEDICINE) with skills in bronchoscopy and management of critically ill patients sought to join busy, moderate-sized, multispecialty group practice. Located 25 miles south of San Francisco, adjacent to 400-bed state-of-the-art hospital. Unsurpassed climate and life-style near city, ocean, and mountain pursuits. Quality educational and employment opportunities for children and spouse. Excellent salary, vacation, and benefits commensurate with experience. Early partnership. Send CV to Number 171, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PSYCHIATRIST. Innovative team working with older adults. Med evaluations, consultations. Some supervision. $78K to $104K plus benefits for full-time. Part-time also available. Denver. National Institute for Behavior Change, (303) 296-2244. Ask for Lois Munson.

PHYSICIANS WANTED

BC PHYSICIANS MANAGED CARE

Cost Care, the nation's leading health care cost management company, is seeking full- or part-time BC physicians to staff the Medical and Mental Health Services departments. Ideal candidates will have:

- Three to five years clinical experience in a managed care setting
- Utilization Review expertise
- Strong interpersonal skills

Send résumé/CV to:

Alan R. Greenfield, MD
VP Medical Services
Cost Care, Inc
17011 Beach Blvd, Ste 400
Huntington Beach, CA 92647

CARDIOLOGIST—NONINVASIVE/INVASIVE to join four member busy cardiology practice in small town, one hour from Los Angeles. Full range of noninvasive cardiology and active Catheter lab. Position available immediately through July 1990. Send CV to Number 175, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and is applying to have an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a paramedic base station and training center and, in addition, has an active helicopter service and regional poison center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr. 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after December 31, 1989. The University of California is an Affirmative Action/Equal Opportunity Employer.

ACADEMIC INTERNIST wanted to teach house staff on clinic and inpatient services at LDS Hospital as a member of its Division of General Internal Medicine. ABIM certification and qualifications for University of Utah faculty appointment required. Must have skills and strong interest in teaching, patient care, and research. Start July 1990. Send CV and three letters of recommendation to Corwin Q. Edwards, MD, Clinic Director, LDS Hospital, 8th Ave and Eighth St, Salt Lake City, UT 84143. An Equal Opportunity Employer M/F/H/V. A Facility of Intermountain Health Care, Inc.

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PHYSICIANS WANTED

DIRECTOR
STUDENT HEALTH CENTER
Oregon State University
Corvallis, Oregon

Physician, MD, responsible for overall management of a comprehensive Student Health Service with staff of eight full-time physicians and approximately 60 other health care professionals and support staff. 16,000 students; $2.2 million budget. JCAHO accredited; inpatient facilities. Must have three years administrative experience in group medical facility, preferably in university setting. Salary competitive plus university fringe benefits program. To apply submit complete résumé with letter of interest stating qualifications for the position and philosophy of student health care to:

Dr Edward Bryan
Director of Housing and Chair, Student Health Center Director's Search
Administrative Services B204
Oregon State University
Corvallis, OR 97331-2135

Three persons familiar with the applicant's medical and administrative experience should be asked to send letters of recommendation directly to the Committee Chair prior to closing date of January 5, 1990. Starting date of June 1, 1990, with some flexibility.

Oregon State University is an AA/EO Employer, complying with Rehabilitation Act of 1973 and responsive to the needs of dual career couples.

INTERNIST BC/BE needed to join busy pulmonary subspecialty practice in rapidly expanding area near Seattle, Washington. Affiliated with 200 plus-bed and expanding hospital. Other subspecialty welcome, but not necessary. Excellent salary with incentive, benefits, office space, and practice support. Send CV and references to Business Manager, Eastside Pulmonary Associates, 1603-116th Ave NE, Ste #112, Bellevue, WA 98004.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful urgent care network. Generous guarantee, incentive plan and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinic, 223 Mt. Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

FAMILY PRACTITIONER, NORTHERN CALIFORNIA. Solo Family Practitioner (including OB) seeks BE/BC associate. English/Spanish preferred. Reasonable call. Beautiful "Redwood Empire" town, two hours from San Francisco. Guaranteed salary, benefits. Contact Andrew Coren, MD, 1165 S. Dora, E2, Ukiah, CA 95482; (707) 463-3663.

NORTH IDAHO. Opportunity for Addictionologist to practice in well established chemical dependency program. Program part of 48-bed, free-standing psychiatric/chemical dependency hospital. Hospital will assist in the establishment of private practice. Hospital located in beautiful Coeur d'Alene, Idaho. Send CV to Chris Cronberg, Administrator, 2301 N. Ironwood Pl, Coeur d'Alene, ID 83814.

Ads Get Results!

PHYSICIANS WANTED

INTERNIST
NEW ORLEANS

Established family health group seeks BC/BE Internist with strong clinical skills, leadership potential. Excellent practice environment, minutes from French Quarter on the Mississippi. Generous compensation, malpractice, relocation assistance. Send CV or call Mr. Lane collect.

HURD/CAMPBELL
100 East Wardlow Road, Suite 100
Long Beach, California 90807
Telephone (213) 595-1101

SANTA BARBARA COUNTY FAMILY PRACTICE

California BC/BE Family Practice Physicians sought by Santa Barbara County Health Department for ambulatory practice in Santa Barbara County. Progressive, up to date, and well supported clinical system. Highly qualified physicians will have two to four years experience in county and/or community based outpatient clinics. Fluency in Spanish is highly desirable. Competitive salary DOE. For more information please send current CV to **Elliot Schulman, MD, Santa Barbara County Health Care Services, 300 N. San Antonio Rd, Santa Barbara, CA 93110; (805) 681-5460.** AA/EOE.

CALIFORNIA: SACRAMENTO. Full-time career position available for BC/BE Emergency Physician in 30,000 visit Emergency Department with base station. Level II, 150-bed facility. Exciting opportunity for membership in prestigious California emergency physicians group which is democratically governed and academically oriented. Send CV to Kate Lawlor, Emergency Physicians' Medical Group, 120 Montgomery St, Ste 1000, San Francisco, CA 94104. ACEP membership preferred.

WANTED: BC/BE FAMILY PRACTICE OR INTERNAL MEDICINE/PEDIATRICS with Emergency Medicine experience for second physician in our Emergency Department. ACLS/ATLS required. Boise offers a variety of cultural activities and is close to skiing, hunting, fishing, white water. Contact Idaho Emergency Physicians with CV at 2312 N. Cole Rd, Ste B, Boise, ID 83704.

PULMONOLOGIST, BC/BE to join multispecialty Internal Medicine group in northern California Sierra foothills (one-half hour from Sacramento, one hour from Lake Tahoe). Guaranteed salary/benefits/malpractice with early partnership. Send CV to Number 177, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTITIONERS AND GENERAL INTERNISTS. Sacramento Kaiser Permanente. Must be BC/BE. Family Practitioners join 23 Family Practitioners with excellent consultant support. Internists work in established Department of Medicine, experience continuing growth. Pleasant practice setting where physicians are free to provide the highest quality medicine with full access to diagnostic and therapeutic services. Affiliated with University of California, Davis, providing a substantial part of their residency programs. Excellent financial package includes in-house CME and retirement package, with no billing or practice management headaches. To join our successful, growing medical group, Family Practitioners send CV to Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825. Internists send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825; (916) 973-5781. EOE.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- **GASTROENTEROLOGY.** Energetic, fully trained associate needed in thriving private practice. Must be skilled in all procedures including ERCP and Sphincterotomy. No investment required. Salary plus percentage/incentives first year, leading to partnership. Malpractice paid. Some Internal Medicine required. 112-bed hospital with Endoscopy Unit.
- **FAMILY PRACTICE.** Guaranteed income while you develop your own private practice in established office. No OB. No investment required.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some Internal Medicine necessary initially. 112-bed full service hospital with excellent ancillary services.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient.

Located in central California near Sequoia National Park, Tulare offers a family oriented environment, abundant and varied recreation, good schools, restaurants, and shopping. Beautiful, affordable homes close to hospital and office. Strong economy. New businesses are contributing to the steady growth of our active community which combines the life-style advantages of a small city with easy access to all California attractions.

Contact:
Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

OREGON—SOUTHERN COAST. Full-time and part-time positions available at Urgent Care Clinic in Brookings, Oregon. Excellent patient mix, non-stressful work environment, and affiliation with Sutter Coast Hospital in Crescent City, California. Rural/resort community, mild climate, beautiful location with immediate access to ocean, mountains, and rivers. Contact Elliot Nipomnick, MD, 100 A St, Crescent City, CA 95531; (707) 464-8511.

NORTHERN AND SOUTHERN CALIFORNIA OPPORTUNITIES. Within one hour of San Francisco or Los Angeles. Outstanding solo, group, and hospital based practices. Positions are salaried and/or fee-for-service. Typical offers include benefits, CME, and moving expenses. Current need is for BC/BE Family Practice, Internal Medicine (all subspecialties), OB/GYN, Orthopedic Surgery, ENT, and Urology. Call or send CV to Ken Baker, The Physician Search Group, 100 Pine St, Ste 2225, San Francisco, CA 94111; (415) 981-7424.

CALIFORNIA, NORTHERN. Full-time Emergency Medicine staff positions available in 230-bed teaching hospital in Stockton with 50,000 annual visits. Teaching programs in Internal Medicine, General Surgery, Family Practice and Obstetrics/Gynecology. Excellent, prompt specialty back-up. Malpractice, health, and dental provided. Flexible scheduling, $100,000 plus annually. Contact Richard N. Buys, MD, PO Box 1020, Stockton, CA 95201; (209) 468-6818. AA/Equal Opportunity Employer.

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PHYSICIANS WANTED

MEDICAL EXAMINER

$80,000 annually, subject to negotiation.

Shasta County, California is seeking to fill the position of Medical Examiner. Approximately 150 autopsies per year performed and there is a staff of five people. It requires possession of a valid California Physicians and Surgeons Certificate and BC in Pathology at the time of appointment.

Redding, the county seat, is a city of 60,000 people located adjacent to the Cascade Mountains in northern California in a semi-rural area. It has outstanding living conditions and a relatively low cost of living.

Contact:
Shasta County Personnel Dept
1500 Court St
Courthouse, Room 105
Redding, CA 96001
Telephone (916) 225-5515

PHYSICIANS WANTED. Under the guise of cost containment, the control of the American health care system is being taken away from us. If you believe in the private practice of medicine, contact Physicians Who Care, 730 N. Main, #624, San Antonio, TX 78205; (512) 226-1400.

INTERNIST WANTED to share practice (part-time) with same in beautiful Bellingham, Washington. Women encouraged to apply. Carletta Vanderbilt, MD, 2950 Squalicum Parkway, Bellingham, WA 98225; (206) 671-7140. Needed by April 1, 1990.

SOUTHERN OREGON. BC/BE Family Practitioner to join busy five doctor Family Practice group summer 1990. Practice is located in the Rogue Valley, which is amply endowed with cultural events and outdoor activities. Affordable housing in area of low seismic potential. Admission privileges available at two local hospitals. OB optional. Guaranteed salary and benefits with option to join group after one year. Send CV to Daniel Heyerman, MD, Central Point Medical Group, PC, 524 Manzanita, Central Point, OR 97502.

SALT LAKE CITY, UTAH, FAMILY PRACTICE PHYSICIAN, BC/BE. Excellent opportunity in Salt Lake suburb to join busy practice, near excellent skiing, hunting, and fishing. Our clinic operates six days a week, and our patients are from a growing Salt Lake suburban population. Excellent salary and benefits. A partnership opportunity will be available after two years. Send CV to Robert Davis, MD, Director, Family Medical Center, 1781 W. 90th S., West Jordan, UT 84092; (801) 562-9100.

BC/BE FAMILY PRACTITIONER / GENERAL PRACTITIONER. Brand new clinic; strong need. Join another Family Practitioner. Diverse practice includes small amount of low risk Obstetrics, optional. Beautiful midwestern community next to many lakes and rivers and just north of the glorious Black Hills mountain range. Outstanding financial opportunity with minimum income guarantee, full benefits, insurance, malpractice, overhead, and relocation expenses. Contact Cheryl Bschor, Jackson and Coker, 400 Perimeter Center Terrace, Ste 760 WJM9, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 288-7030.

SEEKING A PHYSICIAN to associate with a Family Practice group. Ultramodern facility with outpatient surgical suite. Located in Corona, California, between Orange County and San Diego. Growing area. Good climate. We are offering an association with excellent economic advantage. Contact Ann Holmes, (714) 734-3042.

PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists, **Len Nugent and Co, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call** (800) **727-2478, FAX #** (408) **727-7390.** Never a fee to the physician.

NORTHERN CALIFORNIA. Enjoy multitude of recreational opportunities. Beautiful Sierras. Easy access to San Francisco. Four Internists seek associate. Growing community in California's gold country. Rural life-style conducive to family life, yet satisfying specialty practice. Robert Hartmann, MD, 815 Court St, Jackson, CA 95642; (209) 223-3837.

INSTITUTION PHYSICIAN needed to staff the Wyoming State Training School in Lander, Wyoming. We have 360 clients in an institutional setting for acute care in an 18-bed health care center. There is a staff of three physicians and one physician's assistant for total medical services. Attractive benefits, no overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520; or call (307) 332-5302. An Equal Opportunity Employer.

GENERAL INTERNIST/NEUROMUSCULAR/COPD/REHABILITATION. Immediate opening for BC/BE General Internist to join the staff of a 48-bed respiratory unit at an internationally recognized rehabilitation center affiliated with University of Southern California. Management of respiratory-neuromuscular/chest wall disorders, COPD, and tuberculosis. Some critical care. Busy exercise lab. Clinical faculty appointment at USC, depending on qualifications. Interested individuals should send CV to Ahmet Baydur, MD, Chest Medicine Service, Rancho Los Amigos Medical Center, 7601 E. Imperial Hwy, Downey, CA 90242. Equal Opportunity/Affirmative Action Employer.

EUGENE, OREGON. INTERNIST, BC/BE, to join well established 35 physician primary care group. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to Kirk Jacobson, MD, Oregon Medical Group, 1180 Patterson St, Eugene, OR 97401; or call (503) 484-1337.

FAMILY PRACTICE FACULTY NEEDED. Residency program near Los Angeles has full- or part-time openings. Community hospital with university affiliation. Excellent facilities and good benefits with pleasant colleagues. Call Dr Mary Ferris, (818) 500-5594.

MENDOCINO COUNTY. Immediate opening in beautiful coastal northern California for full-time BC/BE General Surgeon with trauma experience. Send CV to Julie Campbell, Mendocino Coast District Hospital, 700 River Dr, Fort Bragg, CA 95437; or call (707) 961-1234.

PSYCHIATRIST

BC/BE, part-time, possibly developing to full-time. Expanding San Francisco bay area practice emphasizing Occupational Medicine and med-legal evaluation seeks consulting Psychiatrist. Outstanding reputation, facilities and support staff, established referral base. Unique income opportunity. Submit CV and letter stating professional goals and availability to:

Personnel
240 Polk St
Box 337
San Francisco, CA 94109

PHYSICIANS WANTED

OREGON

Excellent opportunity for BC/BE General Internist with large multispecialty group in Portland metropolitan area. Group provides comprehensive medical care to 350,000 members of established northwest HMO. Position offers wide range of Internal Medicine and ample opportunity for subspecialty consultation within collegial professional environment. Competitive salary and benefit package, including generous pension program, sabbatical leave, and professional liability coverage. Forward inquiry and CV to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227

CHIEF RESIDENT AND RESIDENT PHYSICIAN II OR III POSITIONS. The University of Nevada School of Medicine is seeking a Chief Resident and several Resident Physician II or III positions with the Department of Internal Medicine. Chief Resident must be eligible for licensure in Nevada. Send letter of application and two reference letters to Stanley Shane, MD, Chairman, Dept of Medicine, University of Nevada School of Medicine, Reno, NV 89557. These positions will remain open until filled. AA/EOE.

CARDIOLOGIST. BC/BE sought to join a large hospital based multispecialty clinic. University affiliated residency program. Interest in echocardiography desired. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

YELLOWSTONE NATIONAL PARK. Physician to cover outpatient clinic, emergency room, and inpatient at Lake Hospital from Memorial Day to mid September 1990. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414; or call (307) 578-2461.

BC/BE FAMILY MEDICINE/INTERNAL MEDICINE needed for well established, comprehensive clinic in sunny San Diego. English and Spanish a plus. Contact Rhonda Simpson, MD, or Marielena Covarrubias, (619) 234-8171, or send CV to Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113. FAX (619) 237-1856.

CENTRAL CALIFORNIA. Join our team of Family Practice Physicians in a progressive community health center near Fresno, California. Competitive salary with extra on-call and overtime. Malpractice paid. Generous vacations and time-off policy. Affiliated with UCSF with on-site Family Practice residents and medical students. Varied practice, including Obstetrics, Pediatrics, and in-patient care with an emphasis on health maintenance, patient education, and primary care research. Position is 60 percent clinical, 40 percent teaching. Bilingual English-Spanish helpful. Contact Ardeth Bier, Fresno County Dept of Health, PO Box 11867, Fresno, CA 93774; (209) 445-3353.

GIG HARBOR, WASHINGTON—INTERNIST. Excellent opportunities in rapidly growing bedroom community for Tacoma and Seattle. Existing medical complex has 19 different health care professionals. Build to suit or finished space available. Information—Dr Jon H. Kvinsland, 5122 Olympic Dr NW, #A201, Gig Harbor, WA 98335; (206) 851-9171.

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PHYSICIANS WANTED

WYOMING. Wyoming's most desirable town is seeking an ENT Surgeon. Located at the foot of the Big Horn Mountains, and serving an area of 35,000, Sheridan, Wyoming is the town that offers both life-style and opportunity. An up-to-date hospital, combined with a young, specialized medical staff provide the basis for an excellent practice. Contact the ENT Search Committee, 1405 W. 5th St, Sheridan, WY 82801.

GASTROENTEROLOGIST — SAN DIEGO. Thriving multispecialty private practice group seeks Gastroenterologist. The practice offers excellent opportunity to enjoy growing group, see private and managed care patients and build stable future. Compensation includes guarantee plus incentives and benefits. Please send CV to Miriam Stephens Drake, 1450 Frazee Rd, Ste 605-1, San Diego, CA 92108; or call (619) 295-0599.

ARIZONA. Established Emergency Medicine group has immediate openings for full- or part-time BC/BE physicians seeking career opportunity in busy Emergency Department with excellent location and case mix. Flexible schedules, excellent living and working conditions. Compensation range $150K to $200K for full-time. Send CV in confidence to General Manager, PO Box 80412, Phoenix, AZ 85060-0412.

INVASIVE CARDIOLOGIST. To join a busy 25 person multispecialty group practice. The setting is in beautiful western Washington between Seattle and Vancouver, British Columbia, Canada. Competitive starting salary and benefit program. Send CV to Shane S. Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

URGENT CARE PHYSICIAN. Full- or part-time position available for northern California urgent care clinic. Contact David Lyons, MD, 900 Oro Dam Blvd, Oroville, CA 95991; (916) 534-9183.

ASSISTANT CLINICAL PROFESSOR. The Department of Neurosciences at the University of California, San Diego seeks individual for July 1, 1990, who has completed residency training in Neurology, fellowship training in Behavioral Neurology, and has experience in care of individuals with dementing disorders. Will serve as Neurologist for a VA Geroneuropsychiatry Unit and federally funded NIA Alzheimer's Disease Research Center. Must possess laboratory skills utilizing molecular neurobiological techniques to determine presence of putative markers in Alzheimer's disease. Experience in conduct of clinical drug trials. Must demonstrate successful research accomplishments by publication in professional journals. Will teach at post-MD and undergraduate medical school levels. Must have MD, California medical license, and Neurology board certification. Salary based on published UCSD pay scale. Send résumé, brief statement of research objectives, and five reference names and addresses by December 31, 1989, to Leon Thal, MD, Professor of Neurosciences, Dept of Neurology, San Diego VA Medical Center, 3350 La Jolla Village Dr, San Diego, CA 92161. The University of California is an Equal Opportunity/Affirmative Action Employer.

GENERAL SURGEON. Coastal northern California. Wonderful opportunity in growing community. Clean air, redwoods. Contact Western Physicians Registry. Carol Sweig or Jim Ellis, directors. (800) 437-7676.

COME LIVE IN THE MOUNTAINS. Internist to share practice/call with three others in attractive small community only 50 miles from Yellowstone National Park. Area abundant in fishing, hunting, hiking, outdoor sports. No state income tax! Generally young, well-trained medical staff with a well-equipped, progressive, newly remodeled hospital. Desire US trained, BC/BE physician, any time between now and summer of 1990. For more information call Ruth McDaniel, CEO, at (307) 578-2489 or send CV to West Park Hospital, 707 Sheridan Ave, Cody, WY 82414. EOE.

PHYSICIANS WANTED

EUGENE CLINIC, EUGENE, OREGON

Dynamic 55 physician multispecialty group with seven locations seeks BC/BE physicians in the following specialties: Dermatology, Family Practice, Geriatrics, Infectious Diseases, Internal Medicine, OB/GYN, Occupational Medicine, Orthopedics, General Surgery (breast disease focus), Urology. Eugene, attractive university town within 60 mile radius of Cascade Mountains and Oregon coast, offers superlative life-style, fine school system, active and varied cultural opportunities, and unlimited recreation. Qualified candidates send CV and three letters of reference to:

Physician Recruiter
1162 Willamette St
Eugene, OR 97401

RADIOLOGIST. Immediate opening for BC General and Diagnostic Radiologist at teaching hospital near Seattle. Ultrasound, CT, and mammography, plus limited basic angiography and interventional skills. Washington license not required. Regular hours. Full-time or six to nine months per year. Five-year contract. Call Dr Bernstein, (206) 840-9652.

PHYSICIAN WANTED. Full-time General Internist/Family Practitioner BC/BE, to join primary care group in San Diego area. Excellent salary, bonus, and benefits. Send CV to Douglas P. Mooney, Medical Director, 1011 Camino Del Rio S., Ste 450, San Diego, CA 92108.

SACRAMENTO KAISER PERMANENTE. BC/BE Family Practitioners needed to join large group of Family Practitioners providing ambulatory and inpatient care in a large prepaid health plan. Excellent working environment with strong specialty support. Outstanding financial package. Sacramento is a growing metropolitan area with good schools and recreational activities. Close to San Francisco and Lake Tahoe. If interested, please contact Stuart Hahn, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825; or call (916) 973-5546. EOE.

SACRAMENTO AMBULATORY / URGENT CARE. Family Practitioners/Internists needed to staff adult urgent care center in Sacramento. Part-time shifts available. Clinic operates seven days per week, 12 hours per day. Excellent hourly remuneration. Benefits possible. Contact Stuart Hahn, MD, (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

PRACTICES AVAILABLE

BEAUTIFUL NAPA VALLEY, CALIFORNIA. Solo Psychiatric practice. Good clientele. Potential for growth as desired. Physician retiring. Residence available. Call David Lucchesi, (707) 552-3831.

WELL ESTABLISHED GENERAL INTERNIST'S PRACTICE. Excellent coverage and income. Silicon Valley. Physician will retire incrementally. U.S. trained BE/BC only, please. Reply to Number 178, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN DIEGO—Family—OB/GYN—General and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, the San Diego professional practice sales specialists, (619) 283-7009.

FAMILY PRACTICE. San Diego East County. Gross over $300,000. Beautifully decorated and well equipped. Practice Consultants, (619) 528-2321.

INTERNAL MEDICINE OR FAMILY PRACTICE. Solo Internist retiring, office adjacent to one of two hospitals in mid-Puget Sound, city of 65,000 in Washington. Rapidly expanding area. Free parking, equipment, records, and experienced personnel available. (206) 252-1088.

PRACTICES AVAILABLE

FAMILY PRACTICE AVAILABLE. Located in desirable Sierra foothills of northern California. Seven year establishment in country setting. Four-day work week, infrequent on-call. Completely equipped four exam room office with EKG, PFT, lab, and surgical equipment, 24-hour cardiac monitor. Large parking area. Close to Sacramento and Lake Tahoe. Average gross $228,000. Asking price $200,000. Please reply to Number 183, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST PLUS NONINVASIVE CARDIOLOGIST. Long established—excellent patient base, San Diego location. Call CBI, the San Diego professional practice sales specialists, (619) 283-7009.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available: Urology, Family, Dermatology, Internal Medicine, OB/GYN, Pediatrics, Ophthalmology, Plastic Surgery, Pulmonology. Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.

LEADING SOUTHERN CALIFORNIA BROKERAGE has all types of medical practices. Will help with financing. Also handles appraisals. Call Angel Gallentine, California Professional Practices, (714) 978-6899.

ORTHOPEDIC PRACTICE AVAILABLE. Excellent opportunity to take over successful, well established practice. 40,000 population regional medical center in Idaho with drawing area of 200,000. State-of-the-art hospital and surgical center. Solo practice, well equipped, well staffed office in new 25 doctor multispecialty center. Excellent referral base. Easy living in beautiful four season country. Negotiable terms. Reply to Number 180, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. Sunny, warm southern California resort town, Palm Springs area. Long established. Practice suitable for Internal Medicine or Family Practice. Two hospitals. Reason: retiring. Great potential and golf! Reply to Number 181, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRACTICE FOR SALE. Internist wanted for established solo practice. Coverage evenings and weekends available. Office adjacent to modern 180-bed acute care hospital. Medical service area 80,000. Please reply to Herbert Waechtler, MD, 980 Trancas, Ste 5, Napa, CA 94558; (707) 224-6556.

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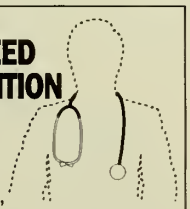

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41st ANNUAL MEETING—SPOKANE SOCIETY OF INTERNAL MEDICINE

March 9, 10, 1990. "Advances in Clinical Cardiology." National faculty, nine hours CME, Ridpath Hotel, Spokane, Washington. Cost: Physician/Nonmember—$75; Physician/Member—$50; Associated Professionals—$50; Residents—$10. Contact **Linda Browne, PO Box 8443, Spokane, WA 99203; (509) 448-2513.**

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 7-9, 1990, Wyndham, Paradise Valley.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 2-7, 1990, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1990, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1990, date and location to be announed.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 26-28, 1990, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1990, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 21-23, 1990, Hyatt, Lake Tahoe.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 4-5, 1990, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1990, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1990, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1990, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 14-16, 1990, Jackson Lake Lodge, Moran.

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